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Original Communications

EDEMA IN PRE-ECLAMPSIA AND ECLAMPSIA*

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THE slight pitting edema of the ankles found in most pregnant patients late in pregnancy may be attributed to the increased venous pressure, as demonstrated by Burwell. Pitting edema over the tibiae is an abnormal occurrence in the absence of varicosities or a previous phlebitis. Edema of the face, hands, abdominal wall, vulva, or body cavities is always an abnormal finding. We have observed that 35 per cent of all types of toxemic patients had no demonstrable pitting edema of the pretibial tissues, and an additional 34 per cent had only slight edema of these tissues.

Studies of the physiology of normal pregnant and toxemic women have been made by us over the past sixteen years. Over 2,700 patients with toxemia have been observed by us, and various examinations have been made in the majority of cases. We believe that our data, as well as those reported in the literature, indicate that the changes incidental to normal pregnancy, namely, an increased capillary permeability and a delayed or impaired water and sodium chloride elimination, are greatly augmented in certain patients, due either to internal or external factors, resulting in an abnormal gain in weight and, eventually, in edema.

Excess salts, water or products of metabolism are eliminated from the circulation by way of the kidneys. If the renal excretion is slow they pass into the tissue spaces, remaining there until they can be excreted. An abnormal amount of water or sodium chloride, either ingested or

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injected parenterally, may thus initiate an edematous or pre-edematous condition. The occurrence of edema should be regarded as a chain of events in which an initial abnormality causes a series of subsequent changes. The various factors in the chain are fairly well recognized, but the primary abnormality and the consequences are still moot points for discussion.

The various primary and secondary factors which may be concerned in the formation of edema in pre-eclampsia and eclampsia are as follows:

1. A decreased colloid osmotic or oncotic pressure of the serum proteins.
2. An increased permeability of the capillary walls.
3. An increased capillary pressure.

Contributory factors, which are of importance, are:

1. A decreased tissue pressure.
2. An increased concentration of proteins in the tissue fluids.
3. A warm environment.
4. An impaired elimination of water or of sodium chloride, or an excessive ingestion of either, or both.
5. An abnormal hormone metabolism.

Edema is likely to occur if the colloid osmotic pressure of the serum proteins is less than 20 cm. of water. Such a low pressure is usually associated with a serum protein concentration of less than 5.5 ± 0.3 Gm. per cent, or a serum albumin concentration of less than 2.5 ± 0.2 Gm. per cent. The average serum protein concentration for normal individuals, based on reports in the literature, is 7.5 ± 0.51 Gm. per cent, with a range of from 6 to 8.3 per cent. A number of observations have been made on the concentration of the plasma or serum protein in pregnant patients. The figures for plasma protein include fibrinogen, which exerts little, if any, osmotic pressure, but amounts to 0.43 Gm. per cent in plasma from pregnant patients. We have, therefore, always determined the concentration of the serum proteins. The average serum protein concentration in normal pregnant patients, calculated from 17 reports, is 6.5 Gm. per cent; the minimum average figure is 5.75, and the maximum is 7.9 Gm. per cent. The average was less than 6.2 Gm. per cent in only two reports.

The figures for serum albumin are not as numerous and range from 2.96 to 4.07, with an average of 3.72 Gm. per cent. The serum globulin range is from 2.2 to 3.83, with an average of 2.90 Gm. per cent. The albumin:globulin ratio ranges from 0.97 to 1.8, with an average of 1.33. Our average serum albumin is 3.66, globulin 3.00 Gm. per cent, and the albumin:globulin ratio is 1.22. In toxemic patients with edema the serum albumin is 3.24 Gm. per cent, and the albumin:globulin ratio is 1.04.

The reported averages for serum protein and albumin concentrations in toxemic patients are listed in Table I. We have calculated the colloid osmotic pressures, with the exception of Strauss' data. The concentrations of both serum protein and albumin are decreased, but with the exception of two, are above the edema level. Strauss' calculated oncotic pressure for eclampsia is less than 20 cm. Harden's data are interesting

TABLE I. REPORTED DATA FOR SERUM PROTEIN FRACTIONS AND COLLOID OSMOTIC PRESSURE IN TOXEMIC PATIENTS

AUTHOR	DIAGNOSIS	SERUM		COLLOID OSMOTIC PRESSURE CALCULATED* CM. WATER
		PROTEIN GM.	ALBUMIN %	
Eastman	Pre-eclampsia	5.4	3.1	22.0
	Eclampsia	6.3	3.5	27.0
	Low-reserve kidney	6.2	3.8	27.0
Plass and Bogert	Pre-eclampsia	5.17		
	Eclampsia	5.77		
Strauss	Pre-eclampsia	5.5	3.1	21.5
	Eclampsia	4.9	2.6	17.5
Harden	1. Pre-eclampsia	6.58	3.81	29.0
	2. Pre-eclampsia	5.60	3.42	23.0
	1. Eclampsia	6.37	3.82	28.0
	2. Eclampsia	4.97	3.16	24.0
Bergman	Edema, slight	6.44		
	Edema, marked	6.04		

*Wells' formula: 1, No protein stabilization; 2, with protein stabilization.

because he stated that if enough protein is ingested to equal the metabolic needs and the protein lost in the urine, the patient improves clinically and the incidence of eclampsia is markedly reduced. His figures for serum protein and albumin concentrations were slightly less in patients who were in "protein stabilization" than in those obtained on admission.

The average colloid pressure in the various reports listed by Drinker and Fields is 35.7, with a range of 26.4 to 46.5 cm. of water, for normal individuals. Only a few figures are available for the determined oncotic pressure in pregnant patients. Runge and Kessler report that it is 36.4 cm. in early pregnancy, and 27.6 at term. Kaboth's figure is 31.5 cm. of water at term.

We have determined the serum protein and albumin concentrations and the colloid osmotic pressure, using Wells' method for the latter determination, in a number of normal pregnant and toxemic patients before and after delivery. Our data are summarized in Table II. We have found that the colloid osmotic pressure is 28.7 cm. in normal pregnant patients at term, 24.9 cm. in toxemic patients with edema, and 26.5 cm. in those without edema. The average calculated pressure for toxemic patients, based on published reports, is 24.9 cm. Oncotic pressures and serum protein determinations were made on the same patients after delivery. These data serve as controls, since the post-partum pressures for normal patients are all within the normal range. Many factors are concerned in the formation and disappearance of edema, but the consensus of opinion is that edema is likely to occur if the oncotic pressure is less than 20 cm., and likely to disappear if the pressure exceeds this figure. The majority of our pressures are above this figure. Furthermore, the determined and calculated osmotic pressures coincide. Therefore, there are no intrinsic changes in the serum proteins, which might account for the edema, as we have postulated several years ago.

TABLE II. SERUM PROTEIN AND ALBUMIN CONCENTRATIONS AND COLLOID OSMOTIC PRESSURE IN PREGNANT PATIENTS

	NORMAL PREGNANCY		TOXEMIC PREGNANCY			
	NO. OF PATIENTS	MEAN	WITH EDEMA		WITHOUT EDEMA	
			NO. OF PATIENTS	MEAN	NO. OF PATIENTS	MEAN
Serum Protein, Gm. %						
Ante partum	15	6.66 \pm 0.06	14	6.34 \pm 0.12	8	6.38
Post partum	12	7.12 \pm 0.05	14	7.12 \pm 0.13		
Serum Albumin, Gm. %						
Ante partum	15	3.66 \pm 0.06	14	3.24 \pm 0.09	8	3.3
Post partum	12	3.81 \pm 0.07	14	3.32 \pm 0.09		
Determined Colloid Osmotic Pressure, cm. water						
Ante partum	15	28.7 \pm 0.64	14	24.9 \pm 0.78	8	26.5
Post partum	12	32.9 \pm 0.56	14	28.6 \pm 0.67		
Calculated Colloid Osmotic Pressure, Wells' formula, cm. water						
Ante partum	15	28.9 \pm 0.52	14	25.9 \pm 0.70	8	27.5
Post partum	12	32.0 \pm 0.47	14	29.1 \pm 0.56		

TABLE III. SERUM PROTEIN CONCENTRATION IN DIFFERENT GROUPS OF TOXEMIC PATIENTS

TYPE OF TOXEMIA	NO. OF PATIENTS	YEAR	SERUM PROTEIN	
			MEAN GM. %	RANGE GM. %
Pre-eclampsia, all patients	36	1933	5.92 \pm 0.08	4.0 - 7.4
Pre-eclampsia, all patients	41	1938	6.43 \pm 0.08	4.6 - 7.5
Pre-eclampsia, edematous	116	1940	6.22 \pm 0.04	4.5 - 7.4
Pre-eclampsia, edema 1 +	12	1940	6.55 \pm 0.08	6.0 - 7.4
Pre-eclampsia, edema 4 +	30	1940	6.22 \pm 0.06	4.6 - 7.4
Eclampsia, all patients	41	1936	6.70 \pm 0.07	5.1 - 8.4
Eclampsia, edema 1 +	19	1940	6.36 \pm 0.12	5.0 - 7.9
Eclampsia, edema 4 +	65	1940	6.37 \pm 0.07	4.5 - 8.5
Vascular-renal, all patients	57	1933	6.36 \pm 0.05	5.0 - 8.4
Vascular-renal, all patients	62	1938	6.71 \pm 0.05	5.1 - 8.3
Vascular-renal, edematous	87	1940	6.67 \pm 0.04	5.2 - 7.9
Vascular-renal, edema 4 +	41	1940	6.09 \pm 0.06	4.6 - 7.6

We have made serum protein determinations on the various groups of toxemic patients listed in Table III. The patients in the 1940 group had varying amounts of pitting edema, and an additional evidence of excessive water retention was that all of them lost at least 12 or more kilograms in weight in the post-partum period. If there was more than one determination of serum protein before delivery, the lowest figure was used. We have omitted all patients with acute or chronic glomerulonephritis, or with marked renal impairment from nephrosclerosis. The post-partum figures for the urea clearance were 74 per cent after pre-eclampsia, 80 per cent after eclampsia, and 70 per cent for the vascular-renal disease group, indicating normal renal function. A further division of patients having a 1+ edema, and those with a 4+ edema, was made, but it showed no correlation between the serum protein concentration and the amount of edema. The means for pre-eclampsia and

eclampsia were 6.22 and 6.36 Gm. per cent, respectively. These figures, as well as the fact that only 16 per cent of the pre-eclamptic, and 12 per cent of the eclamptic patients had a serum protein concentration of 5.5 Gm. or less, indicate that the cause of the edema in over 80 per cent of our toxemic patients is not due to a hypoproteinemia.

TABLE IV. PERCENTAGE OF PATIENTS WITH SERUM PROTEIN CONCENTRATION OF LESS THAN

	GRAMS PER CENT		
	5.0	5.6	6.0
Pre-eclampsia	4	16	39
Eclampsia, edema 1 +	0	11	37
Eclampsia, edema 4 +	5	12	37
Vascular-renal disease, edematous	0	6	18

The average serum protein concentration at two weeks post partum for the same patients was 6.85 ± 0.05 for those with pre-eclampsia; 6.85 ± 0.06 for those with eclampsia, and 7.1 ± 0.04 for those in the vascular-renal group.

We have believed for many years that the edema was not due to a hypoproteinemia, and we have repeatedly stated that a marked blood dilution occurred preceding clinical improvement, associated with an average *decrease* of 14 per cent in the serum protein concentration in pre-eclampsia, and 25 per cent in eclampsia; and that the diuresis, disappearance of the edema, negative sodium chloride and water balance, and greatest weight loss occurred when the serum protein concentration was lowest.

An increased permeability of the capillary wall has been suggested as the cause of certain types of edema. The capillary wall may be injured by prolonged anoxemia or by certain poisons; for example, those apparently associated with acute glomerulonephritis and epidemic dropsy. Some toxin or hormone which alters the capillary wall may be the primary cause of the edema found in pre-eclamptic patients. Unfortunately, there are no measurements for directly determining the capillary permeability.

Petersen and Lash have attempted to detect changes in the capillary permeability by an indirect method. They have determined the protein content of blister fluid and have noted that the amount of protein is increased in pregnant and edematous patients. Our results varied, but, generally, were confirmatory in a small series of patients. Unfortunately, this method is painful.

Lash, using the intradermal salt solution test, found that the wheal disappeared more rapidly in pregnant than in nonpregnant patients, and that the time of disappearance was shorter on the leg than on the forearm. In the toxemias of pregnancy, the disappearance time became extremely short and was due presumably to the high protein content of the subcutaneous fluids. The test is simple and striking, but all types of edema in pregnancy gave similar results.

Landis states that the average arteriolar capillary pressure is 45 cm. of water, and the venous capillary pressure is about 22 cm. Reported observations in pregnant patients are at variance. We believe that all the data at hand indicate that in both normal and pregnant toxemic patients the arterial capillary pressure is within the normal range.

The venous capillary pressure is dependent largely on the venous pressure. If the latter becomes too high, the capillary pressure will exceed the oncotic pressure of the serum proteins and fluid will not be absorbed from the tissues. Thomson, Reid, and Cohen reported no change in the arm venous pressure in pregnant women. They found, however, in a small group of toxemic patients, that more values fell within the upper normal range.

Burwell has reported that the average venous pressure in pregnant patients at term is 9.0 for the arm, and 20 cm. for the leg. He found the average venous pressure in nonpregnant individuals to be 5.8 cm. for both the arm and the leg. He observed that this difference in pressure began at the fourth month of pregnancy and slowly increased throughout pregnancy, but that after delivery the leg venous pressure fell rapidly to normal. He studied these pressures in pregnant bitches and found comparable changes to those observed in pregnant women. He noted that if the intra-abdominal pressure became increased by the injection of salt solution, the leg pressure also increased. He did not ascribe much importance to this observation in the human individual because the abdominal wall is never as tense as it is in the experimental animal. If the gravid uterus was supported so that it did not press on the pelvic veins, the pressure in the femoral veins decreased, although it still remained above that in the jugular veins. He attributed this remaining increased pressure to the effect of the placental circulation, which resembles an arteriovenous fistula.

Landis and his co-workers have demonstrated that fluid accumulates in the tissue spaces when the venous pressure is greater than 15 to 20 cm. of water. Increased temperatures also resulted in a greater filtration rate, which accounts for the increased incidence of edema in pregnant patients in hot weather.

Thompson, Thompson, and Dailey have demonstrated that when the human subject stands quietly the blood volume is diminished by as much as 400 c.c., as fluid filters from the blood into the tissues of the legs. This fluid contains relatively little protein, so that the protein percentage of the circulating blood rises while the subject stands still. This phenomenon may explain some of the discrepancies in reported observations of serum protein concentrations in various conditions.

Youmans and co-workers have studied the serum protein concentration, colloid osmotic pressure, and leg volume in normal individuals. They found that standing at an angle of 75 degrees for approximately one hour caused an increase of from 18 to 40 per cent in the concentration of the serum protein, and an increase of from 29 to 65 per cent in the colloid osmotic pressure of the blood in the foot of normal subjects. The increase in the concentration of protein and in the osmotic pressure was approximately twice as great as that which occurred in the blood from the arm. The volume of the leg increased from 3.11 to 4.87 c.c. per 100 c.c. of leg, but pitting edema did not occur in any of the normal subjects. Patients with nutritional edema showed essentially similar changes, with a demonstrable increase in pitting edema. Calculations based on the data obtained suggest that the increase in the tissue pressure was from three to five times as important in limiting the loss of fluid from the blood, as was the increase in the colloid osmotic pressure.

We have obtained blood from an arm vein in a small number of edematous pregnant patients at rest in bed, and then blood from the arm and foot after the patient had had her legs hanging out of bed for ninety minutes. The difference in the arm cell volume and the serum protein concentration may amount to as much as 19 and 23 per cent, respectively; and the difference between the resting arm blood and the hanging leg blood may amount to as much as 9 per cent for the hematocrit, and 21 per cent for the serum protein. This method of determining the rate of filtration in the legs caused by an increased venous pressure may be of value in detecting potential pre-eclamptic patients.

Keys and Taylor have demonstrated that during severe work the blood becomes concentrated, due to the movement of the filtrate, which is low in protein, from

the blood into the tissues. They found that although the serum protein concentration increased, the colloid osmotic pressure definitely decreased. They concluded that the filtrable protein must be approximately at least five times as active osmotically as nonfiltrable protein. Their observations, as well as the preceding ones, indicate the value of bed rest in the treatment of edema and toxemia.

Burch and Sodeman state that the average tissue pressure in normal subjects amounts to 17.9 mm. of water. Using their method, Brown and myself, in a small series of patients, have found that the tissue pressure is increased slightly in normal pregnant patients, and markedly in those with edema. An even greater rise in the tissue pressure, caused by an increase in venous pressure, due to an arm band exerting a pressure of 40 mm. of mercury, demonstrated an increased permeability of the capillaries.

The following observations indicate that in normal pregnant patients the water and salt metabolism is abnormal, and that the renal function is altered, if not actually temporarily impaired. These changes in physiology in normal pregnant patients require but little added alteration to become pathologic. Once edema forms, a vicious circle has been started, which may terminate in the development of eclampsia.

Slemons noted that the ratio of urine to ingested fluids was less during pregnancy than in the puerperium or in the normal individual.

Holtermann found that 25 per cent of the pregnant women without edema, who were tested with Kaufmann's method, showed latent edema. He concluded that the latent edema in these women was not due to heart disease, but to an increased permeability of the capillaries.

Theobald and Verney have stated that pregnant women near term secreted more urine at night than during the day, but that when these women remained in bed the output of urine was constant. Animal experimentation demonstrated that the upright position favored the stagnation of blood in the lower extremities, due to gravity and the absence of muscular contractions. This stagnation leads to an increase in venous and capillary pressure and, consequently, to loss of fluid. Thus, late in pregnancy the fluid which filters into the tissues of the legs during the day, re-enters the circulation and is excreted at night. They state that if the fluid which escapes into the tissues by day is excessive and is not presented to the kidneys for secretion by night, edema of the tissues, commencing in the lower extremities, will occur.

Janney and Walker have noted that the pregnant patient at term excretes approximately 67 per cent of the usual normal output of ingested water. After delivery the excretion soon increases to 100 per cent. In a small series of toxemic patients, the excretion dropped to 17 per cent of the normal. These observers also found that the kidneys were far more efficient with the patient in the horizontal than in the vertical position.

We have confirmed their findings in a small series of normal patients at term. A group of toxemic patients showed an even more marked oliguria. In many instances the patients secreted no urine for the first hour of the test.

Sondern and Harvey have observed in normal pregnancy that after phenol-sulphonephthalein injection the time for the appearance of the dye was increased and the average two-hour excretion was decreased.

We have noted that the mean for the urea clearance is 102 per cent before, and 125 per cent after delivery, and that the normal pregnant woman is able to excrete urine with an average specific gravity of only 1.022 after a fifteen-hour fast. The average specific gravity increases to 1.030 after delivery. The low specific gravity in pregnancy is due to a decreased amount of solids, especially urea and chlorides. All specimens of urine obtained on admission from 26 patients with eclampsia

were concentrated and highly colored, but contained an average concentration of sodium chloride of only 0.185 per cent. In 12 patients with pre-eclampsia the average concentration of sodium chloride was 0.169 per cent. The urea nitrogen was also usually less than 500 mg. per cent.

The excretion of large amounts of ingested sodium chloride or of potassium chloride are delayed in normal individuals. Torbert and Cheney found that the daily ingestion of 50 Gm. of sodium chloride for two days resulted in a decrease of 10 per cent in the hematocrit, and 15 per cent in the serum protein concentration in one subject. The colloid osmotic pressure decreased 39 per cent in one, and 31 per cent in the other subject. On the second day, edema of the face and ankles was noted.

Rupp found that the excretion of sodium chloride is delayed in pregnant women, and that the excess chloride is stored in the tissues, which appear to have an unusual affinity for it. He reports that there may be a dry retention of chloride and for that reason he advises a restriction of chloride rather than of fluids. Rupp believes that there must be some alteration in the capillary permeability and states that it is really the sodium ion which is the active agent in causing the edema.

Lundin and Scharf state that the salt and water metabolism are connected inseparably, both in normal and in pathologic conditions. They note that the administration of large amounts of sodium chloride caused a comparatively small sodium chloride retention in normal sheep, but a marked retention occurred in pregnant sheep.

Harding and Van Wyck have demonstrated that the daily ingestion of 15 Gm. of sodium chloride by a normal nonpregnant or pregnant woman results in a large positive water and salt balance. The weight increases and the serum proteins decrease in the concentration. Slight edema may occur. Similar therapy in a group of toxemic patients, whose edema had subsided on a salt-poor diet, resulted in a return of the edema in all of the patients, and an increased blood pressure and the recurrence of blurred vision and headache in some. The intravenous injection of 300 c.c. of a 10 per cent solution of sodium chloride had no effect on the normal pregnant woman, but in the borderline or mild toxemic patients it caused a rise in the blood pressure and a marked increase in the proteinuria. In an eclamptic patient, it caused a recurrence of the eclampsia. They conclude that excessive amounts of sodium chloride are definitely injurious to toxemic patients. They stated that a salt-poor diet is of great importance in the treatment of pre-eclampsia, and advised that the diet of normal pregnant patients should be salt-poor every fourth week as a prophylaxis against the development of pre-eclampsia.

Thompson and Pommerenke carried out a very careful water and electrolyte balance in three pregnant women. They found an average retention of sodium amounting to 14.7, and of potassium amounting to 7.9 milliequivalents. The chloride balance in one patient was 1.2, in the second it was 4 milliequivalents, and in the third it was negative. They noted a very close parallelism between the chloride and sodium balance. The potassium balance varied less than sodium or chloride, and there was no correlation between sodium and potassium.

Freyberg and his co-workers studied the caloric intake, nitrogen, water, and sodium balance of a patient during the last two months of pregnancy. They found that the sodium balance was positive for almost every day of the test, and the retention ranged from 0.132 to 0.22 Gm.

Coons and her co-workers report a daily mean retention in normal pregnant patients of 0.877 Gm. of chlorine, 1.265 Gm. of sodium, and 0.508 Gm. of potassium.

Thorn, Nelson, and Thorn have found that there is a retention of water, sodium, and chlorine in women at the intermenstrual and premenstrual periods, when the

level of the sex hormones is high. They also found that estrone, administered to dogs, caused a water retention and an increased elimination of potassium.

Taylor and his co-workers have studied the sodium and potassium balances and the excretion in the urine of prolactin, pregnanediol, and the estrogens, in 4 normal pregnant patients and 2 pre-eclamptic patients. They concluded that sodium is retained in pregnancy and the puerperium during a high estrogen concentration, and is lost during periods of diminishing hormone concentrations. There was no correlation between the potassium balance and the hormone level. It is interesting to note that the patients showed a maximum sodium and potassium excretion about the second to the sixth day of the puerperium. Our findings are similar, indicating that there has been a marked storage of electrolytes in the extracellular fluids. One patient showed a marked negative balance in the ante-partum period, as we have also demonstrated repeatedly. Our criticism of Taylor's work is that he compares exact measurements of the total sodium and potassium intake and output with the approximate determination of the hormones in the urine. They assume that the excess of hormones in the urine is due to an overproduction, but the same factor, or factors, concerned in the negative electrolyte balance may also account for the marked excretion of the hormones. In other words, we have noted that not only are sodium and chlorine retained in the edema fluid, but that urea, phosphate and other metabolic products are stored in the fluid. It is just as reasonable to believe that the hormones also may have been stored in the tissue fluids and that the correlation is accidental.

Taylor and his co-workers, in a recent extensive study of hormonal changes in pre-eclampsia and eclampsia, have reviewed the literature and have concluded that: "The tests for these hormones give only approximate values. The blood and urinary figures for these substances show large normal variations when different individuals are compared and even when different specimens of the same individuals are contrasted. The hormonal changes observed in the toxemic patients are perhaps associated with the cause of the toxemia, but may simply be the result of the disturbance of kidney, liver, or placental physiology."

Improper nutrition, anemia, and hookworm disease favor the formation of edema. We have had a number of edematous pregnant patients with hemoglobins of from 3 to 8 Gm. per cent, in whom the edema disappeared if the hemoglobin was increased to 11 Gm. per cent by blood transfusion. All of these patients had serum protein concentrations above the edema level and, with the exception of several with a borderline hypertension, were otherwise normal. Balfour stated that 2.93 per cent of the natives delivered in his hospital in India had a severe anemia, characterized by fever, tachycardia, gastrointestinal disturbances, albuminuria, and edema.

Wickramasuriya stated that the incidence of toxemia was increased in the Hindu with anemia due to hookworm disease. Ross and his co-workers at Duke University report that their patients with edema and eclampsia have had a diet markedly inadequate in proteins, and some had low serum protein concentrations. Arnell, at the Louisiana State University, states that he has observed true nutritional edema in pregnant patients, but that marked edema, as a complication of hookworm anemia, is more common. The incidence of toxemia in the patients of this latter group is not materially increased.

The ante-partum hematocrit figures for edematous patients with pre-eclampsia, eclampsia, and vascular-renal disease are 37.4, 44.0, and 37.0 volumes per cent; and the post-partum figures are 38.1, 38.4, and 39.8 volumes per cent, respectively. The mean hematocrit figures for normal pregnant patients at term are 37.3 ± 4.2 , corresponding to a hemoglobin of 11.6 Gm. per cent. Therefore, anemia was not a factor in causing edema in our toxemic patients.

Leiter and Fahr, and Kerkhof and Giere have demonstrated that edema will not develop in dogs with serum protein concentrations of 3 to 4 Gm. per cent, unless the animal is given adequate amounts of sodium chloride and water. Observations at various clinics indicate that the edema of pre-eclampsia or eclampsia may be, as a rule, cured by eliminating from the diet one of the chief constituents of edema fluid, namely, water, sodium, or chloride. The consensus of opinion is that the curtailment of sodium chloride presents fewer difficulties and causes less discomfort to the patient than the restriction of water.

Arnold believes that eclampsia and pre-eclampsia are due to cerebral dysfunction, caused by an abnormal retention of water. He dehydrates his eclamptic patients by restricting the fluid intake, by administering saline cathartics, by repeated spinal drainage, by the intravenous injections of hypertonic glucose solution, and by venesection. The pre-eclamptic patient is treated by restricting the fluid intake and by the use of a low salt diet.

Jerlov, in a large group of toxemic patients, finds that the restriction of salt is the most important dietary precaution in both preventing and treating toxemia. He also restricts meat to two or three times per week in toxemic patients, and advises boiling the meat rather than roasting it.

De Snoo states that he has been able to almost eliminate eclampsia from patients in his clinic by the use of a salt-poor diet. He also follows the urinary output of chloride for its prognostic value.

Bland and Bernstein found that in pre-eclamptic toxemia the blood pressure is not influenced by bed rest and a regular diet. A salt-free diet resulted in a decrease in the blood pressure in all cases. The chloride excretion in the 24-hour urinary output served as a criterion for treatment. The success of their treatment depended upon maintaining the urinary chloride below 1 gm. A salt-free diet led to the disappearance or amelioration of all the symptoms or signs and to a marked loss in weight.

We have been using a salt-poor diet in the treatment of toxemia of pregnancy, with excellent results. Our sodium chloride balance studies were started in 1926. The intake of sodium chloride, to be of any therapeutic value, must be restricted sufficiently so that the twenty-four-hour excretion of sodium chloride in the urine is less than 3 Gm. Our low sodium chloride diet contains 0.715 Gm. of sodium, 1.42 Gm. of chloride, 2.61 Gm. of potassium, 0.95 Gm. of calcium, 1.47 Gm. of phosphorus, 62 Gm. of protein, 76 Gm. of fat, and 229 Gm. of carbohydrate. The eclamptic diet, consisting of fruits and fruit juices, contains 0.74 Gm. of sodium, 1.69 Gm. of potassium, 1.06 Gm. of chloride, and is used for a period of from five to seven days.

Strauss stated that in edematous pregnant patients the calculated colloid osmotic pressure and the total plasma proteins were decreased, and concluded that the latter was due to a low protein intake. He stated that the edema disappeared if the patient was given an adequate amount of protein, vitamin B, liver extract, and a sodium-poor diet. Three of his patients with hypoproteinemia and edema in the first pregnancy developed low serum protein concentrations in the next pregnancy, despite a high protein intake. They did not, however, develop edema because they were kept on a salt-poor diet. In his last paper he stated that the loss of weight in edematous patients occurred without any change in the plasma protein level and was initiated by the administration of a diet low in sodium.

Tillman, discussing Strauss' work, stated that he was not in agreement that the edema was responsible for the toxemia of pregnancy, and that he has repeatedly seen edematous pre-eclamptic and eclamptic patients with normal serum protein concentrations.

Stander, discussing Strauss' paper, stated that in his belief a lowered serum protein is not the cause of edema in pre-eclampsia and eclampsia.

Zangemeister was the first to describe the abnormal retention of water in pregnant women (hydrops gravidarum), which was associated with albuminuria and convulsions in a few cases.

Fink, in 1921, discussed hydrops gravidarum and stated that it was possible for edema to be present without an increase in the blood pressure or kidney findings. The formation of edema, according to him, was favored by the intake of salt and acid foods. He does not believe that the subcutaneous tissues maintain a strict isotonicity, as does the blood, and that excess sodium chloride may be stored. He believes that eclampsia is due to cerebral edema.

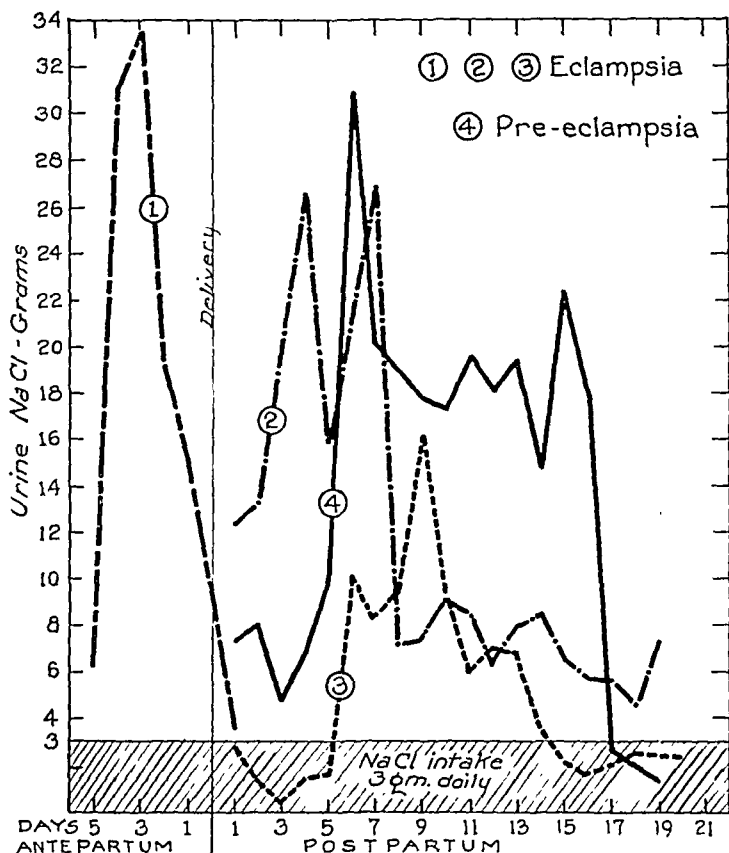


Fig. 1.—Patient 1: Negative sodium chloride balance of 99 Gm. (equivalent to 16 kilograms of water), with loss of 9 kilograms in weight. Patient 2: Loss of 164 Gm. (equivalent to 27 kilograms of water), with loss of 50 kilograms in weight. Patient 3: Loss of 37 Gm. (equivalent to 6 kilograms of water), with loss of 20 kilograms in weight. Patient 4: Loss of 204 Gm. (equivalent to 34 kilograms of water), with loss of 41 kilograms in weight.

Heynemann believes that the capillary damage is of major importance in causing eclampsia. He ascribes the edema to an increased permeability of the capillaries, but does not know the primary cause for the damaged capillary endothelium.

In Fig. 1 we have presented data on three eclamptic patients and one pre-eclamptic patient. Each patient had a tremendous negative chloride balance, a marked diuresis, and a marked loss in weight. There is some correlation between the amount of chloride excreted and the weight lost. For example, Patient 4, who had a negative sodium chloride balance of 204 Gm., corresponding to 34 kilograms of water, lost 41

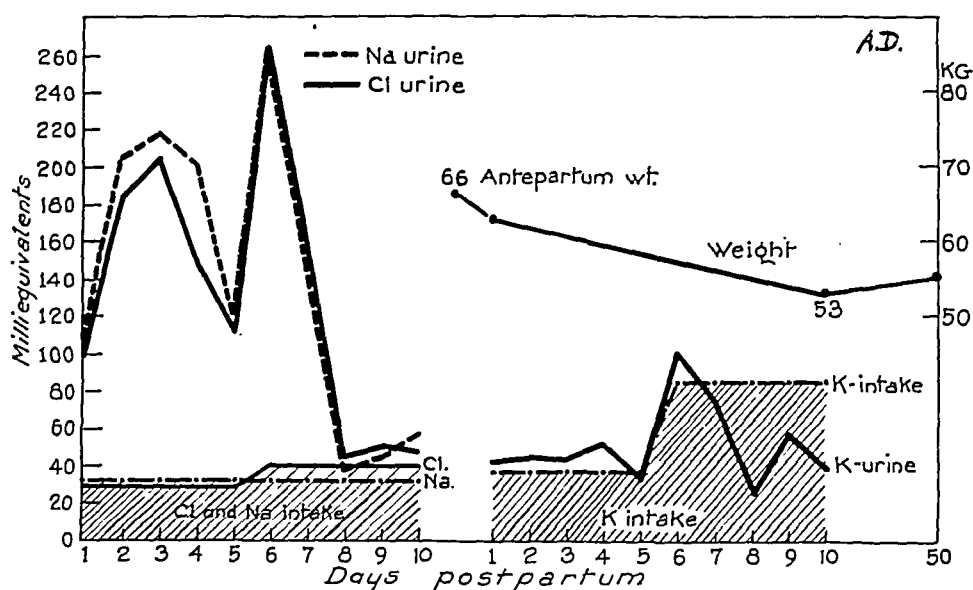


Fig. 2.—Graph of patient on eclamptic diet for first five days, and on a low sodium diet for the next five days. Fetus weighed 2,000 Gm., and the amniotic fluid and placenta were assumed to have weighed 1,000 Gm., giving a total weight loss of 3,000 Gm. at delivery.

$$\text{Milliequivalent} = \frac{\text{Grams of electrolyte}}{\text{Molecular weight of electrolyte}} \times 1,000.$$

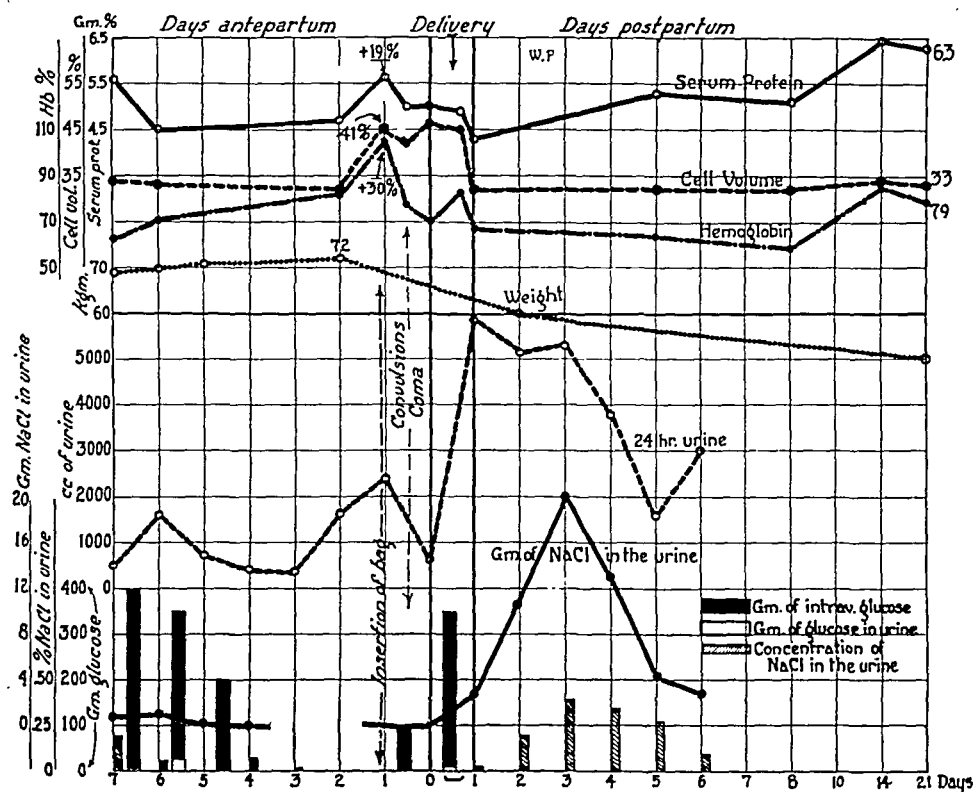


Fig. 3.—Graph illustrating the changes in the chloride and water balance, weight, serum protein, and hematocrit in a pre-eclamptic patient who did not respond to treatment and who ultimately developed eclampsia. The retention of chloride, as demonstrated by its absence from the urine, and the simultaneous gain in weight are noteworthy.

kilograms in a period of nineteen days. The loss in weight and the water loss, calculated on the sodium chloride excretion, do not coincide. Experiments are now in progress to determine if a better correlation occurs between weight loss and measurements of the extracellular body water. However, no potassium determinations were made on these patients, and, although the edema is presumably extracellular, we believe that the muscle cells may share in the abnormal retention of water in some patients.

A large amount of water could be held in the muscle cells of the body without the patient showing any demonstrable edema. This phenomenon would account for those patients whose weight gain is so rapid that it must be due to a retention of water and yet no edema can be detected. Furthermore, if this water were quickly released from the cells, it would account for the sudden appearance of edema noted in many eclamptic patients, and for the occasional development of symptoms and signs of acute cardiac decompensation in toxemic patients. We hope that further balance studies of sodium, potassium, and chlorine, and the determination of the extracellular body water may help us to determine if intracellular edema can occur.

We have noted that the potassium excretion usually parallels the chloride and sodium excretion as long as they are negative. This is illustrated in Fig. 2. The chloride and sodium excretions usually parallel each other, and in this patient they were almost identical. The negative balance for these substances indicated that there had been considerable retention. The chloride excretion was equivalent to 9 kilograms of water, and the patient lost 10 kilograms. The negative potassium balance may have been due either to a washing out of potassium along with the sodium, or to an intracellular edema. Similar studies on other patients yield identical results.

Fig. 3 illustrates a sodium chloride retention despite the diet, bed rest, and intravenous injections of hypertonic glucose solution. The urine became chloride-free and the weight increased markedly. Labor was induced, but no precautions were taken to prevent a blood concentration, and eclampsia developed. The chloride and water excretion were marked after delivery and the weight decreased 12 kilograms in twenty-one days.

Fig. 4 is presented to illustrate the relationship between edema, the clinical findings, and the changes in the serum protein concentration and the cell volume. With a low sodium diet we were able to produce a marked negative balance of sodium chloride, associated with a weight loss of 8 kilograms in a period of nine days. During this time a blood dilution occurred, with the serum protein concentration decreasing to 5.1 Gm. per cent at about the height of the diuresis. Coincidental with the negative chloride balance, the edema diminished and the blood pressure also decreased. The blood became concentrated at the time of delivery, and in the post-partum period there was a second dilution during the diuresis.

Analyses of the twenty-four-hour specimens of urine from edematous post-partum patients for inorganic ash, total base, phosphate, nonprotein

and urea nitrogen, and titrable acidity reveal that the excretion of these substances roughly parallels the excretion of sodium and chloride, indicating that the edema fluid also contained these various substances.

Some patients gain weight excessively in each pregnancy and may develop edema, but, as a rule, no other symptoms or signs appear. We have studied these patients over a period of years, and they have always had normal blood and urine findings and a normal renal function. It is obvious that these women have difficulty in excreting sodium chloride because they do not gain excessively on a rigidly controlled sodium-poor diet.

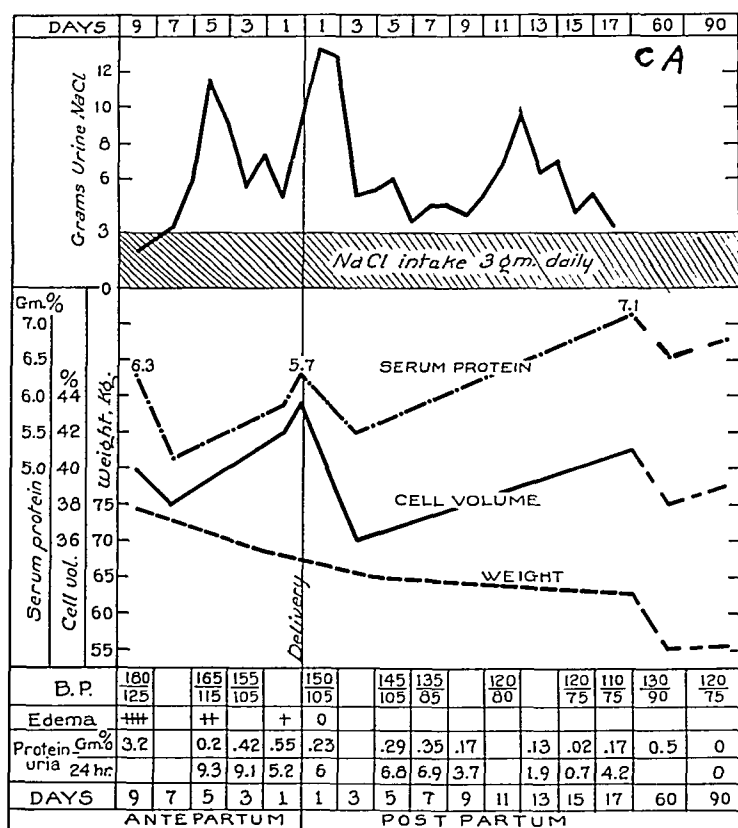


Fig. 4.—Graph depicting the typical ante-partum and post-partum changes in serum protein, hematocrit, chloride excretion, edema, blood pressure, and weight loss in a patient with pre-eclampsia. The marked ante-partum excretion of chloride and clinical improvement indicate the beneficial effects of bed rest and a proper diet.

That pregnancy has a very definite effect on capillary permeability and water balance is exemplified by studies of two pregnant patients with diabetes insipidus who, despite their polyuria, showed excessive gains in weight and developed pretibial edema and a mild hypertension. Their serum protein concentrations were 6.5 and 5.5 Gm. per cent, respectively, at the height of the edema.

CONCLUSIONS

The following physiologic changes occur in normal pregnancy:

1. The venous pressure in the legs is increased and causes an increased loss of fluid from the blood into the tissues of the legs.

2. There is an increased capillary permeability.
3. The elimination of water and solids by the kidney is delayed or impaired.
4. The average serum protein concentration is 6.5 Gm. per cent.
5. The average colloid osmotic pressure of the serum protein is 28.7 cm. of water.

Pre-eclampsia and eclampsia may occur if these changes are of greater magnitude than normal, or if they are exaggerated by internal or external factors. Thus we find the following in these diseases:

1. Greater alterations than normal in the venous and capillary pressures and capillary permeability.

2. The average serum protein concentration in edematous patients with pre-eclampsia is 6.22, with eclampsia it is 6.7, and with vascular-renal disease and normal renal function it is 6.67 Gm. per cent.

3. The average colloid osmotic pressure of edematous pre-eclamptic patients is 24.9, and of toxemic patients without edema it is 26.5 cm. of water.

4. The retention of sodium, chlorine and water is greatly increased in some pregnant patients, resulting in an abnormal gain in weight, and, finally, in demonstrable edema.

5. Changes in the concentration of the female hormones are apparently associated with edema, but whether this is the cause or the result cannot be stated from our present knowledge.

6. The prevention and treatment of edema are dependent on the limitation in the diet of the principal components of edema fluid, namely, sodium chloride and water. The curtailment of sodium chloride in the diet presents fewer difficulties and causes less discomfort to the patient than the restriction of water.

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URINARY INCONTINENCE RELIEVED BY RESTORATION AND MAINTENANCE OF THE NORMAL POSITION OF THE URETHRA*

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INTRODUCTION

A VERY sharp distinction must be made between urinary incontinence and urinary urgency or frequency lest we operate upon a patient with urgency and frequency who has no incontinence and find that after operation she still presents these symptoms but is really continent. We must keep the confidence of, and be frankly honest with, a patient having incontinence. We should clearly explain to her that sometimes the first operation may be unsuccessful and a second will be required. I hope to make the reasons for the above remarks clear. This paper is a presentation of a few facts and experiences which I have acquired since my previous publications¹⁻³ have appeared. By noting my failures and mistakes and studying carefully the histology, it has been possible to report progress and, at the same time add more clarity to the problem.

It has been shown by Goff⁴ and clearly confirmed by me that the bladder and ureters (including the trigone) lie loosely upon the vaginal wall, while the urethra lies in very intimate contact with the anterior vaginal wall. Microscopic cross section shows the levator mus-

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cle fibers (Fig. 1) originating from the periosteum of the symphysis near the midline do not pass beneath the urethra but pass posteriorly and insert their ends into the lateral wall of this part of the vaginal cuff, thus creating the "dimple" of the vestibule. The anterior vaginal wall consisting of smooth muscle fibers intermingled with connective tissue passes below the urethra from the region of one "dimple" to the opposite "dimple." The vaginal wall extends from one end of the urethra to the other in intimate contact with the outer coat of the intrinsic structure of the urethra. The vaginal wall thus constitutes a table on which the urethra rests in intimate relationship. This fact has been utilized with satisfactory result in one case, described further on in the paper.

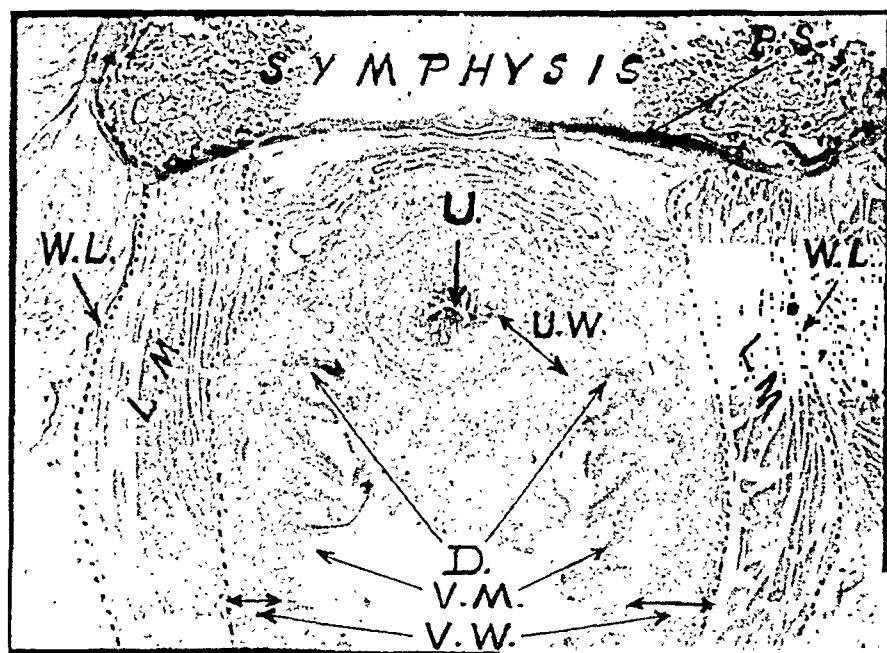


Fig. 1.—Photograph of a microscopic section cut at right angles to the urethral canal, through the urethra, vagina, and the symphysis, to show the vagina and insertion of those levator fibers nearest the midline. *U.*, urethral canal and mucosa; *U.W.*, urethral wall; *D.*, "dimple"; *V.M.*, vaginal mucosa; *V.W.*, vaginal wall; *W.L.*, white line; *P.S.*, periosteum of the symphysis; *L.M.*, levator muscle (within the dotted area). Note (1) the origin from the periosteum of the symphysis and from the white line, and the insertion into the walls of the vagina; (2) the arrangement of muscle and vaginal wall to form the dimple; (3) note that none of the levator fibers pass beneath the urethra.

THE NORMAL URETHRA

The normal urethral mechanism in action can be studied with the aid of radiographs, and from these a comparison of the damaged urethra is made possible. Two hundred cubic centimeters of a 3 per cent solution of sodium iodide are instilled into the bladder. The sac, to outline and distend the urethra, is put in place and connected with a manometer containing 25 per cent solution of sodium iodide, and the manometer raised so that its fluid level is 30 cm., or 12 inches above the urethra when the radiograph is taken. While a radiograph is being taken, the patient lies on her back (or side, for lateral views) and is

asked to "hold," to "relax," or to "void" as the case may be. In this article "relaxing" means that the patient directs no exertion upon the bladder or urethra but lies perfectly still; "holding" means that she uses all her voluntary efforts to prevent urine from escaping from the urethra; and "voiding" that she uses all her voluntary efforts to force urine from the urethra. Fig. 2 is a composite picture of a radiograph of the normal bladder and urethra while "voiding," superimposed upon a radiograph of the same taken while "relaxing." One notes, when in the "relaxed" state, the small amount of dilatation of the sphincter surrounding the internal meatus, the normal position of

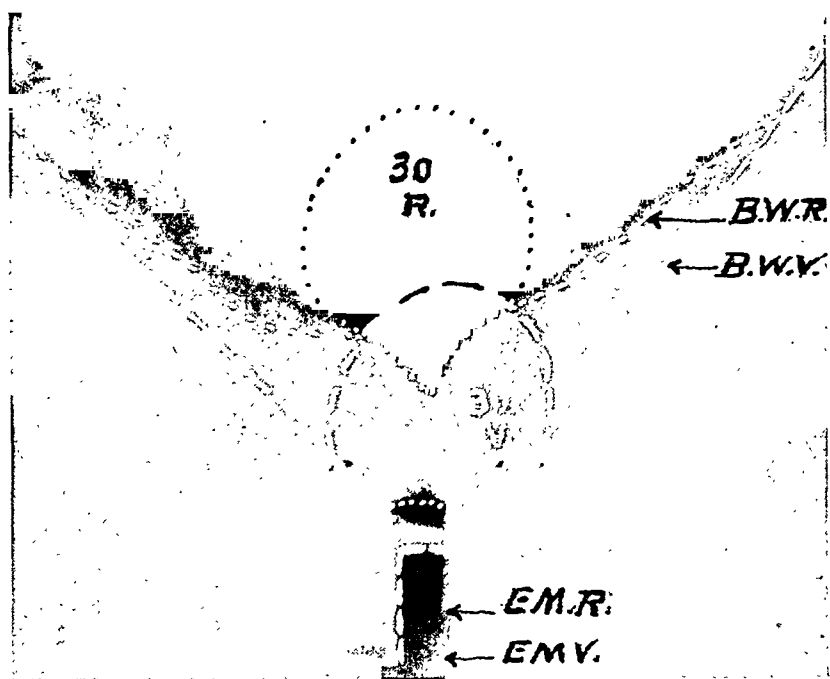


Fig. 2.—The normal urethra in the "relaxing" and "voiding" state (composite picture by superimposing two radiographs). 30 R., The sac outlining the urethra and bladder in the "relaxing" state; 30 V., the sac outlining the urethra and bladder in the "voiding" state; B.W.R., bladder wall, "relaxing;" B.W.V., bladder wall, "voiding;" E.M.R., external meatus, "relaxing;" E.M.V., external meatus, "voiding."

Note: In the "voiding" state (1) the bladder floor is pushed down between the rami; (2) the inner part of the sphincter is dilated; (3) the urethra is pushed out of the pelvis; (4) the position and shape of the urethra permit all the urine to escape from the bladder.

Note: When incontinence is present, the urethra and bladder in the "relaxing" state will assume some permanent position between the two positions shown above. Greater incontinence will exist the nearer the extreme "voiding" state is approached.

the floor of the bladder, and the position of the external meatus relative to the symphysis. In the "voiding" state, by comparison, the bladder floor seems to have been pushed down between the rami, the inner half of the urethra dilates widely (in fact its diameter appears to be the same diameter as the sac, 2 cm.) while the outer half dilates very little, and the external meatus of the urethra has been pushed endwise out of the pelvis about 1 cm. Fig. 3 (anteroposterior view) is a radiograph illustrating the normal urethra in the "holding," "relaxing," and "voiding" states. In the "holding" position (Fig. 3, A),

little deviation from the "relaxing" position occurs. The voluntary effort on the part of the patient does not pull the urethra far into the pelvis, nor does it much diminish the diameter of the sphincter about the internal meatus, but the external meatus is drawn about 1 mm. into the pelvis. On the contrary, the "voiding" position (Fig. 3, *C*) compared with "relaxing" position (Fig. 3, *B*) shows the sphincter about the internal meatus to be much dilated and the whole urethra to have been pushed endwise more than 5 mm. out of the pelvis. Fig. 4 (lateral view) is a radiograph illustrating a normal urethra in "relaxing" and "voiding" states. The distance the external meatus has been pushed

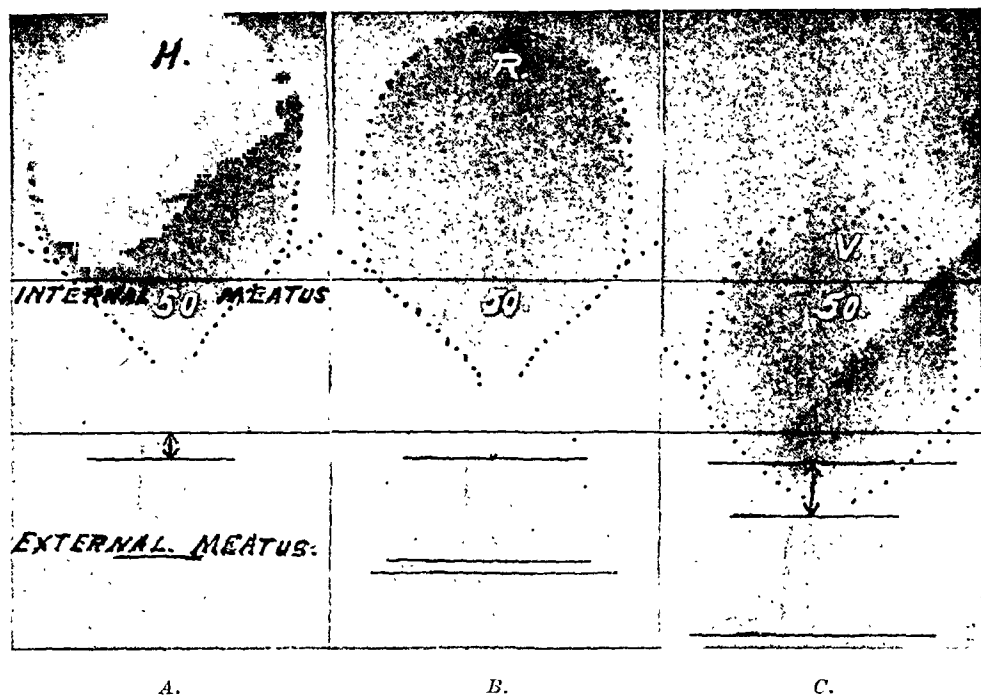


Fig. 3.—Radiographs of the urethra and bladder, anteroposterior view normal urethra. *A*, In the "holding" state (*H.50*); *B*, in the "relaxing" state (*R.50*); *C*, in the "voiding" state (*V.50*). In the "holding" state, the sphincter about the inner third of the urethra is closed a little tighter and the external meatus is drawn a short distance within the pelvis as compared to the normal "relaxing" state. Hence, by position, one would say the "relaxing" state should function almost as efficiently as the "holding" state. Directly opposed to this in the "voiding" state, the sphincter about the inner third of the urethra is much dilated, the bladder is pushed in direction down and out of the pelvis and the external meatus is pushed nearly a centimeter out of the pelvis as compared to the "relaxing" state.

out of the pelvis while "voiding" varies with each patient, the one illustrated being about 1 cm. Another observation one makes is, that less than 1 cm. in length of the sphincter from the internal meatus takes part in the dilatation when "voiding." The urethra is pressed downward into the vagina along with the bladder. One interesting fact which is observed when the sacs are superimposed (Fig. 4, *B*) is that during "voiding" no fluid leaves the sac, although it is perfectly free to do so. One deduces from this that the fluid pressure in the bladder is not increased when voiding, but, that only the exit of urine is made easier. Fig. 5 (lateral view) illustrates the behavior of a large cystocele: First, when "relaxing," second (Fig. 5), when a

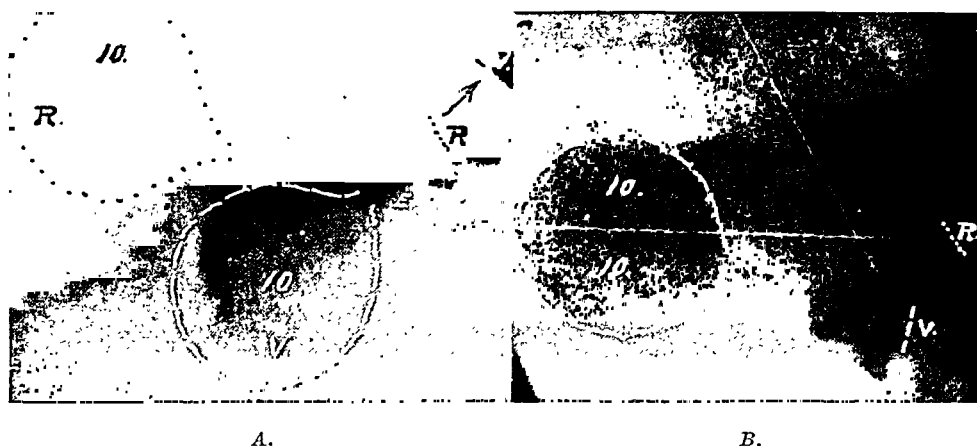


Fig. 4.—Lateral view, normal urethra. A, Sac 10.R showing position of urethra and bladder in the "relaxing" state and R, the position of the external meatus; sac 10.V showing the position of the urethra and bladder in the "voiding" state, and V, the position of the external meatus. Note: (1) The bladder and the urethra have been pushed downward and forward into the vagina. (2) The closed portion of the urethra has been shortened about one-fifth in the "voiding" state and the remainder of the sphincter has dilated. (3) The external meatus has been pushed outward and downward from within the pelvis. B (Sacs in A superimposed). The sac does not change its size any appreciable amount in the "voiding" state.

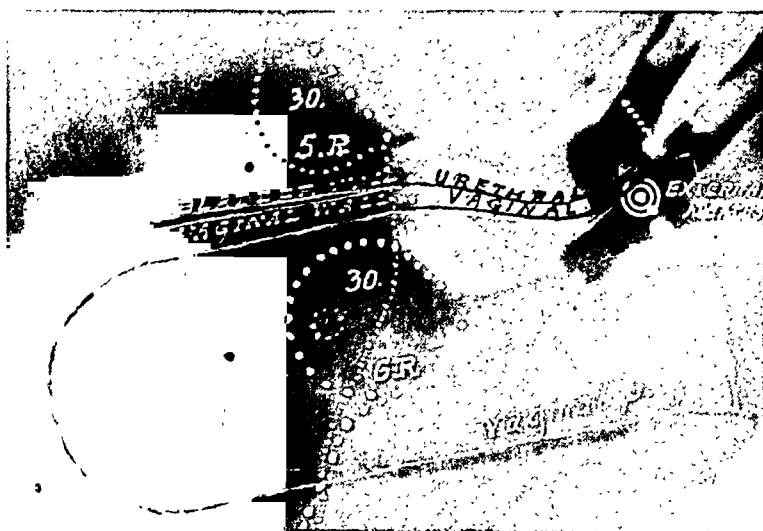


Fig. 5.—Two radiographs superimposed, lateral view, the urethral sphincter being only slightly relaxed. There was a very large cystocele which on straining would balloon out of the vagina. The first radiograph was taken in the "relaxing" state, sac 30.6R outlining the relation of the bladder and urethra. The shaded portion represents the dilatation of the sphincter about the inner third of the urethra and the double circle the external meatus. The second radiograph was taken in the "relaxing" state with a Sim's vaginal plug in the vagina, sac 30.5R outlining the relation of the bladder to the urethra, and the line of dots above the double circles indicate the external meatus. The Sim's plug has lengthened the urethra, the external meatus being more external to the pelvis and the internal meatus more internal. The sphincter about the inner third of the urethra appears completely closed. The urethra and bladder have been raised in the pelvis. These are the requisites for continence. The Sim's plug has effected a lengthening of the urethra, by what means it is impossible to say. This lengthening theoretically should greatly increase the sphincteric power of control.

Note: The lines between "bladder wall" and "vaginal wall" indicate the plane which the bladder and the urethra rest upon when the Sim's vaginal plug was in the vagina.

Sims' vaginal plug is inserted in the vagina, and third, when "voiding" (Fig. 6). This patient had a mild incontinence, losing a drop or two of urine only when coughing or sneezing. The features presented by this are (1) that the sac contains less fluid when the bladder is high, hence the urethra is longer and the internal sphincter is more tightly closed; (2) that the middle and inner thirds of the urethra in the "voiding" state can be turned through an angle of 90 degrees to lie between the labia and the sphincter mechanism can continue to function in this position; (3) that in "voiding" this urethra is pressed endwise out of the pelvis about 0.5 cm. Since there is comparatively



Fig. 6.—Two radiographs superimposed, lateral view; same patient as in Fig. 5. The first radiograph was taken in the "relaxing" state, sac 30.6R outlining the relation of the bladder to the urethra. The shaded portion represents the dilated portion of the sphincter about the inner third of the urethra, the double circle the external meatus. The second radiograph was taken in the "voiding" state, sac 30.7V outlining the relation of the bladder and urethra, and the dashes the external meatus. The urethra has become angulated, the inner half having turned through 90° from the "relaxing" state. The external urethra has been pushed almost 0.5 cm. out of the pelvis. The length of the urethra is about the same as in the "relaxing" state, therefore, there is still continence. The bladder and part of the trigone lie outside the vagina. Where the ureteral orifices are cannot be conjectured. The urethra itself has scarcely assumed any of the "voiding" state contour, a fact which coincides with the difficulty encountered in voiding by a patient with a protruding cystocele.

little support from the vaginal wall beneath the urethra, we must consider that there is little or no sphincteric control offered by the support, and practically complete control is in the intrinsic sphincter mechanism.

URETHRAL STATE AND INCONTINENCE INTIMATELY RELATED

Since the normal urethra in the "relaxed" state at all times maintains its contour and position and prevents any urine from escaping from the bladder, and the same urethra in the "voiding" state permits all the urine to run out of the bladder, one can deduce that the patient with incontinence has a urethra with some permanent degree of the "voiding" state. Now, (1) the continuous loss of sphincter muscle tone or the permanent distortion of that portion of the sphincter muscle surrounding the inner third of the urethra produces various degrees of the permanent

voiding state and must always be present for incontinence, while (2) a vaginal wall which has stretched below the bladder and urethra and (3) a urethra which has been moved more external to the pelvis may or may not be present. Loss of sphincter muscle tone may appear with increasing age, and relaxation may be responsible for incontinence in a nulliparous woman.

FACTORS CONTRIBUTING TO INCONTINENCE

A number of factors have been previously mentioned and will not be repeated here. Cases are briefly cited to illustrate other contributing causes:

CASE 1.—A patient having urinary urgency and frequency, and doubtless some degree of incontinence, was referred by her general practitioner to a urologist. By cystoscopic examination the urologist found a few urethral polyps, and he removed them by electrocoagulation. From this time on, the patient had a persistent incontinence.

CASE 2.—Another patient, referred to a urologist, had a number of urethral caruncles which he vigorously cauterized. The result was a marked intermittent incontinence persisting for several months.

CASE 3.—Another patient, about 55 years of age, unmarried, had a pelvic cellulitis, probably followed by bladder and urethral adhesions as a child, and developed a severe constant incontinence for several months.

CASE 4.—A patient, married, nulliparous, about 58 years of age, had a constant moisture from the vagina, diagnosed by two gynecologists as hydrorrhea, but a third gynecologist diagnosed the condition as one of incontinence with a relaxed vesical sphincter developing several years before operation.

CASE 5.—Another patient, after a plastic operation for moderate lacerations and mild incontinence had a large mushroom catheter jerked from her urethra on the eighth postoperative day by an interne, and she became markedly incontinent.

CASE 6.—Another, a young woman, delivered a medium-sized baby after a five-hour labor terminated by forceps. She became persistently incontinent. The cause, here, was a urethrovaginal fistula at the junction of the middle and inner thirds of the urethra, associated with a lateral distortion of the inner third of the urethra by a dense band of scar tissue pulling the inner third of the urethra over to the right ramus. Three operations had been done upon this patient before I saw her.

CASE 7.—In a multiparous patient with moderate lacerations of the anterior and posterior vaginal walls I did a Kelly operation for incontinence together with an operation for cystocele, rectocele, and laceration of the pelvic floor which was a failure. Incontinence was worse than before.

CASE 8.—A multipara with some prolapse, extensive cystocele, and rectocele had marked incontinence for years. Trauma at labor was the cause of her incontinence.

TRAUMA OF LABOR

As the size of the fetus and uterus increases, the space for the bladder between the symphysis and the uterus correspondingly diminishes. The bladder can take care of this physiologic condition in two ways, either by a frequent emptying of itself, or, by lateral distention into the paravesical spaces (the latter can be seen by radiographic study

of the bladder). The lower uterine segment broadens laterally, but there may be little change in the size of the anterior vaginal wall. The bladder and ureters lie loosely upon this floor of vaginal wall.

Labor sets in, the cervix dilates, and the anterior vaginal wall is stretched laterally to some degree as the head descends. In some instances the head produces a contusion of the bladder and the anterior vaginal wall, which on healing causes the bladder to become fixed to the vaginal wall, either on part or all of one side, or, in some cases almost completely. A second labor will then stretch both the bladder and the vaginal wall, and if this stretching is carried forward in the midline, the posterior urethra and bladder wall may become thinned out. If carried still farther along the floor of the bladder, the fibers of the urethra and the vaginal wall of the vestibule will be split, allowing the urethra to

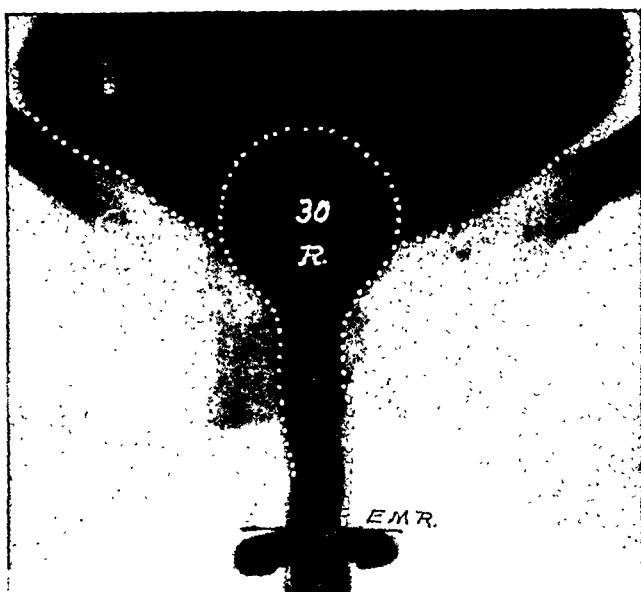


Fig. 7.—Radiograph, "relaxing" state, failure at operation, cause not known. *Note:* One sees here a marked relaxation of the sphincter mechanism from one end of the urethra to the other, several weeks following my operation. Dr. Daniel Mishell repeated my operation a few weeks later with complete success.

drop into the vagina and at the same time be pushed a short distance out of the pelvis. Should the damage be between the urethra and the ramus, its healing may leave connective tissue, permanently distorting the urethra. These urethras assume certain degrees of a permanent state of voiding.

FAILURES AND THEIR SOLUTION

Failures have occurred and I have been able to get some valuable information from a careful study of them. The cases cited serve to illustrate:

CASE 1.—A patient, 55 years of age, unmarried, was found to have extensive adhesions between the bladder and the vaginal wall, between the urethra and bladder and both rami. My method of operation was done, but the patient was still incontinent. Fig. 7 shows the bladder to be in good position; there is some dilatation of the inner third of the urethra and a marked dilatation of the middle and

outer thirds of the urethra. The reason for the failure is not known but it is different from other cases. Repetition of my operation by Dr. Daniel Mishell resulted in normal control.

CASE 2.—Another patient with cystocele, some prolapse, a rectocele, and lacerated pelvic floor who had a plastic operation which included my technique for incontinence, unfortunately had a moderate infection of the anterior wall as a postoperative complication. Fig. 8, *A*, shows the fall of the bladder wall and a marked dilatation of the sphincter about the inner third of the urethra. There was a bilateral failure of maintenance following restoration. This patient has not been reoperated upon.

CASE 3.—A patient, 25 years of age, was delivered four years ago of a 7½-pound child in a five-hour labor terminated by forceps. She lost control of her urine from that time on. She does not know whether she had a damaged bladder or urethra. An attempt was made three months later to restore continence without success. Two later attempts by a urologist also failed. Whether the original incontinence was due

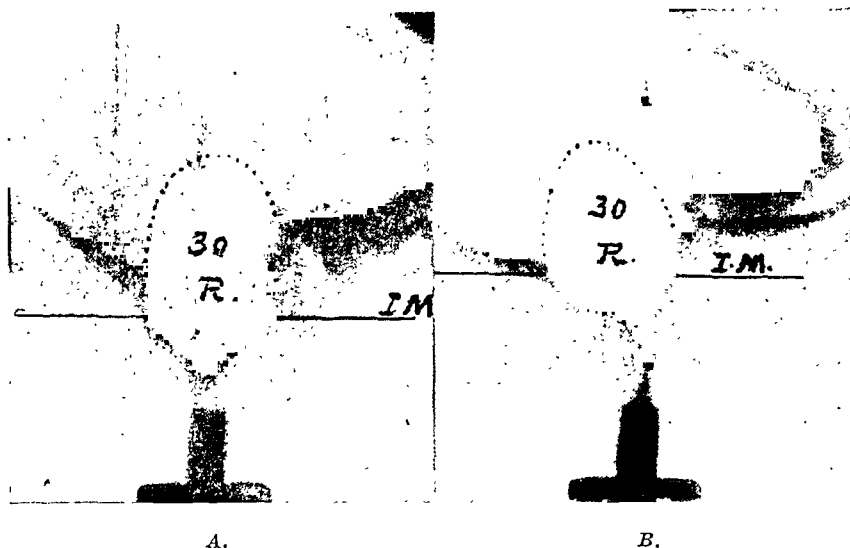


Fig. 8.—Failures at operation. *I.M.*, internal meatus. *A*, Radiograph of a urethra and bladder following my operation. There was a postoperative infection in the anterior vaginal wall. The urethra and bladder walls probably returned to their original preoperative positions. Restoration was accomplished without maintenance. This shows a bilateral failure of maintenance. *B*, Radiograph of a urethra and bladder following my operation. The right border of the trigone had to be separated from the right ramus by sharp dissection, during which procedure the bladder was entered. Restoration was accomplished but infection set in. The right urethra and bladder returned to the position which they occupied before operation. This shows a unilateral failure of maintenance.

to a urethrovaginal fistula, is not known, but probably it was. The pediatrician taking care of the child referred her to me. A fistula, about 2 mm. in diameter, having its opening into the vestibule of the vagina about 1 cm. to the right of the midline and 2 cm. from the external meatus, made its way backward and medially in an oblique course into the urethral canal by an opening about 1 cm. from the internal meatus. A ureteral catheter was passed through the fistula into the bladder. During withdrawal a cystoscope was used to follow the end of the ureteral catheter to the internal meatus, and a urethroscope to follow it until it disappeared. The opening was located about 1 cm. from the meatus. Hence, about 1 cm. in width of the sphincter of the inner third was beyond the fistula. This portion of the sphincter, if normal, should have prevented urine from escaping through the fistula when the patient was recumbent. But she was always wet. Therefore, this portion of the sphincter was inefficient. The cause, found during dissection, was a dense scar about 1 mm. thick and 4 mm. wide, holding the wall of the urethra well over to the right ramus posterior to the fistula. This patient had both a fistula and a distorted urethral sphincter. Had only the fistula been excised and closed, the patient

would not have been relieved. The fistula was dissected out, its opening closed to evert the urethral mucosa into the canal, the scar band cut, the urethra completely freed from both rami and my incontinence operation completed. The patient now has normal control of her urine. One must conclude that the liberal or complete dissection is the conservative one, when the end result is our goal.

CASE 4.—In some cases the trauma of labor relaxes or disengages the normal support of the urethra, so that it assumes the position which the normal urethra takes during the act of voiding. One such patient had a normal dissection of the vaginal wall from the urethra and the bladder, extending over to the ramus pubis on each side, and Kelly sutures were placed. She had more incontinence

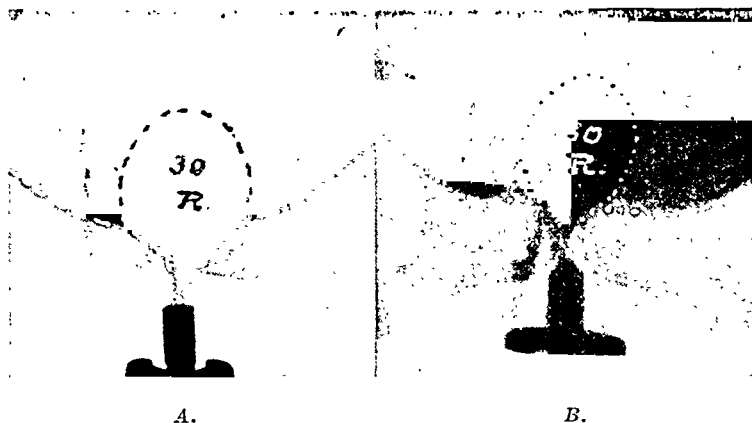


Fig. 9.—A, Radiograph of a bladder and urethra following a Kelly operation resulting in failure. B, Radiograph of the same bladder and urethra following my operation some months after, resulting in success.

Note: The procedures in both operations were almost identical, except that in my operation separation of the bladder and urethra from both rami and replication of the bladder and urethra by a second row of interrupted sutures were added procedures.

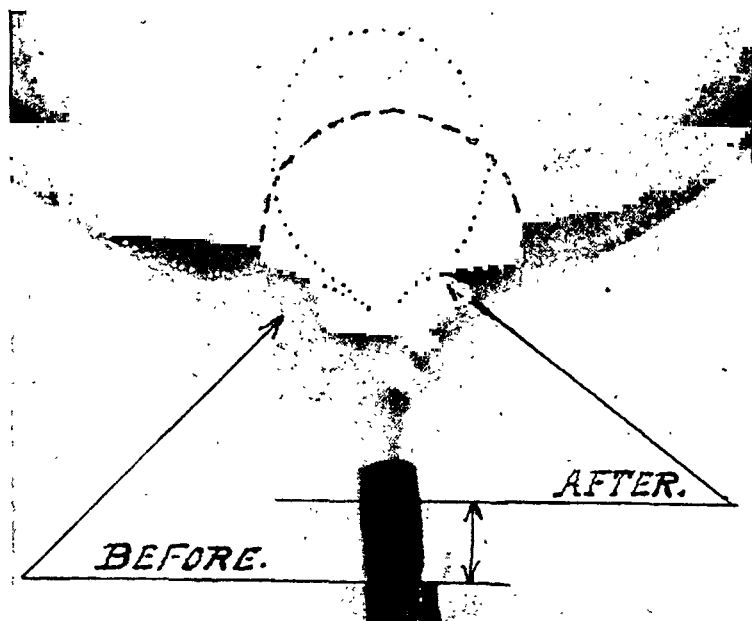


Fig. 10.—Radiograph 9A, superimposed on radiograph 9B, to show the relative position of the external meatus, the urethra and the bladder, after the Kelly before and after procedure. Before my operation the urethra and bladder have the contour of the "voiding" state during relaxation, but after operation the "relaxing" state is restored during relaxation. This is the requisite for continence.

than before. A urethral radiograph illustrates the result, Fig. 9, *A*. The operation after the method which I described was then done, after which she obtained normal continence. A second radiograph, Fig. 9, *B*, illustrates the end result. Superimposed radiographs before and after operation (Fig. 10) correspond identically with radiographs (Fig. 2) of the normal urethra while relaxing and voiding. The first operation showed no restoration of the urethra but the second operation restored it into the pelvis so that the sphincter mechanism appears normal.

CASE 5.—Let us analyze one more case first reported by my technique in a previous article. This patient, whose operation was a complete failure, was a multiparous woman with prolapse accompanied by a large cystocele, a moderate rectocele, and incontinence for a number of years. She was operated upon in November, 1936. At operation, the bladder and urethra had to be removed from the right ramus by sharp dissection, and in so doing, the bladder was entered just to the right of the trigone. This was immediately closed; then my operation for incontinence was completed. Infection set in between the anterior vaginal wall and the bladder. The anterior wall broke down and on the tenth postoperative day (a retention catheter still being in the bladder) the bed became continuously wet and so persisted for five days, after which the bed was dry. The fistula, fortunately, healed spontaneously and remained so until she went home. She returned two days later, being continuously wet. Intravenous indigo carmine was watched for in the vagina but none appeared while plenty escaped from the urethra. The plicated urethra and bladder had slipped. The infection had produced a solution of the sutures and the urethra partly took on its original contour, Fig. 8, *B*. There was a unilateral failure of maintenance following restoration. The result was a complete failure. During the next year some improvement was obtained by treatment. Cystoscopic examination was done; the ureteral orifices were normal, there were a mild posterior urethritis and a moderate depression of the trigone. In February, 1938, fifteen months after the first operation, she was reoperated upon, repeating the first operation. The end result was better, the patient could be dry from one-half to three hours at a time. Cystoscopic examination revealed the ureteral orifices normal, the right side of the trigone normal, a mild posterior urethritis and a red raised mound about 2 cm. in diameter situated between the internal meatus and the left ureteral orifice. Attached to the base of this was a dense band about $\frac{1}{2}$ cm. in diameter which was attached to the left ramus. Vaginal traction on the band revealed distortion of the trigone laterally, when viewed through a cystoscope. The right side of the trigone was now normal but the left side was tethered to the ramus by an adhesion. I studied my failures and found that some degree of infection between the anterior vaginal wall and the bladder and urethra was the apparent cause. This infection, rapidly dissolving the plicating sutures, permitted all or part of the urethra to resume its original position and adhere again. Doubtless, the seat of this infection was the serum in either paravesical space or between the bladder and urethra and the vaginal wall. To avoid this would probably mean fewer or no infections, and if the hypothesis were right, then more or all successes would follow. How was this to be done? Since the anterior vaginal wall of the vestibule is in intimate contact with the urethra, would it be possible to allow the vagina to granulate under the urethra? The most complete way would be to leave each paravesical space open into the vagina, to leave the plicated urethral wall wide open to agglutinate quickly and wait for the vaginal mucosa to granulate over the lower surface of the urethra and bladder. Eleven months after the second operation (in January, 1939) the patient was reoperated upon. The urethra and bladder were again completely separated from the ramus, the band between the left trigone and the ramus removed. The urethra and bladder walls were plicated and replicated. The vaginal flaps were turned back into the paravesical spaces and lightly held there by packing. The patient had an uneventful convalescence. The vaginal mucosa grew over the lower surface of the bladder and urethra to re-line the vestibule. The patient was allowed to go home on the twenty-sixth postoperative day, having complete control of the urine. Last week, sixteen months after her third operation, she was seen in the follow-up clinic and she stated she can go eight hours without voiding and now never loses a drop of urine.

From this case the following observations are made:

1. Adhesions formed after each of the first two operations must be attributed to something happening which let the urethra and bladder as a whole, or in part, resume its original damaged position and again adhere to the ramus or the vaginal wall.

2. It was most probable that adhesions following the first operation were the result of the infection which caused the break-down of the vaginal wall.

3. It was most probable that the band of scar tissue following the second operation was due to the reorganization of a simple or an infected hematoma which formed between the trigone and the ramus.

4. Since the urethra after the third operation remained in place and was continent without any floor on which to rest during the time the vaginal roof of the vestibule was filling in with granulations, the logical deductions would be (a) that freeing the urethra, then plicating and replicating the urethral and bladder walls is sufficient to replace it to the position of the normal "relaxing" urethra; and (b) that the replacing of the urethra in this manner enables the intrinsic sphincter mechanism to function normally; and (c) the anterior vaginal wall beneath the bladder and the urethra (as far as the urinary tract is concerned) is simply a protective floor on which the bladder and urethra are supported.

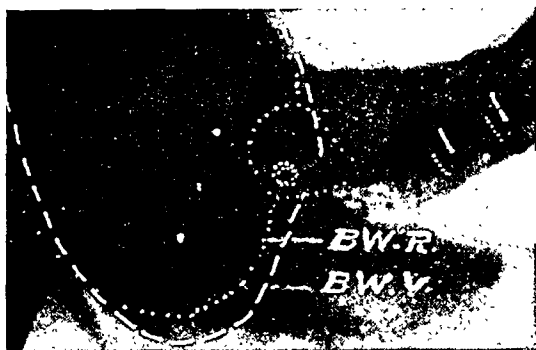


Fig. 11.—Radiograph after my operation on a bladder and urethra, in the "voiding" state (B.W.V.) superimposed upon the same bladder and urethra in the "relaxing" state (B.W.R.). The "voiding" state is almost identical with the "relaxing" state. The nearer the "voiding" state approaches the "relaxing" state, the more efficient the continence will be.

Now it seems rather drastic to leave the dissected flap of the vaginal wall separate from its opposite mate, so I have for some time been using the Y drain of rubber tissue, one end placed in each paravesical space, as used by Dr. G. G. Ward in his cystopexy operation, and obtaining satisfactory results.

You may well ask, does this operation do what I claim for it? One patient, twice operated on by me, using the Kelly operation, had two successive failures. The third operation 5½ years ago by my method was successful and is satisfactory to this time. Fig. 11 (lateral views) taken over seven weeks after the successful operation shows that, both in the "relaxing" and the "voiding" state, her urethra quite meets the requirement of the normal urethra.

CONCLUSIONS

1. The normal urethra in its "voiding" state is pushed down with the vaginal wall into the vagina, its external meatus is pushed endwise out of the pelvis by varying distances up to 1 cm., and the sphincter muscle surrounding the inner third of the urethra dilates.

2. A varying degree of the "voiding" state (which becomes permanent following relaxation or injury) is present when there is persistent incontinence; the greater the degree the greater the incontinence.

3. When there is no permanent dilatation of the inner third of the sphincter, the urethra may undergo excessive degrees of motion without any incontinence. However, persistent displacement may in time permanently overstretch the inner third of the sphincter, when incontinence will develop.

4. The sphincter mechanism functions with its greatest efficiency when its greatest length is restored, when it is restored as far as possible within the pelvis and restored as high as possible above the vagina.

5. To fulfill the restoration of the urethra it is first necessary to completely separate the urethra from all attachments to the vaginal wall and the rami, both of which, following injury, will hamper the function of the sphincter mechanism.

6. After completely freeing the urethra, restoration of the sphincter mechanism can be satisfactorily accomplished by plicating and replicating the under surface of the bladder and urethra.

7. The sphincter mechanism, unhampered by any lateral tractive forces after restoration, will perform its normal function.

8. The sphincter mechanism probably requires no assistance of the levator muscle fibers, and the vaginal wall beneath the bladder and urethra is only a protective floor on which the bladder and urethra lie.

9. Any factor such as infection or hematoma beneath the restored urethra may dissolve the plicating sutures and allow the urethra in whole or in part to resume some degree of the "voiding" state, thereby producing a failure, and re-operation will be necessary. For success, restoration must be bilaterally maintained. Maintained restoration can best be accomplished by very free drainage of the paravesical spaces and open vaginal wall flaps.

10. The success of any incontinence operation will be measured by the fulfillment of the restoration herein described and the maintenance of that restoration.

I wish to thank Dr. A. H. Aldridge, Chief Surgeon of the Woman's Hospital, and Drs. George F. Hoch, Inglis F. Frost, Arthur J. Murphy, and Daniel Mishell for their assistance and interest in this work; Dr. Harriet McIntosh for her x-ray contributions and Dr. Joshua W. Davies for his anatomic interest in the problem.

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ARE ESTROGENS CARCINOGENIC IN THE HUMAN FEMALE?*

THE EFFECT OF LONG-CONTINUED ESTROGEN ADMINISTRATION UPON THE UTERINE AND VAGINAL MUCOSA OF THE HUMAN FEMALE

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THE experimental production of genital and breast carcinoma in rodents and mice by means of estrogens has raised the very important question as to whether there might not be some danger of inducing carcinomas in human beings by the therapeutic administration of estrogens. In the normal female, the genital tract undergoes periods of growth and proliferation followed by periods of regression and rest. This is most strikingly illustrated in the cyclical morphologic changes of the endometrium. Menstruation is followed by a gradually increasing tempo of growth of the endometrium, culminating in the shedding associated with menstruation. These recurring phenomena are dependent upon the cyclic production of adequate amounts of estrogenic hormone by the ovaries. In the human female, furthermore, cessation of ovarian activity is followed by a discontinuation of the cyclical proliferative phenomena in the endometrium and by an advancing regression and atrophy in the endometrium and vaginal mucosa. It is significant, however, that regardless of how atrophic the endometrium or vaginal mucosa may appear microscopically, these structures can be stimulated, by the administration of adequate amounts of estrogenic hormone, to regenerate to a state very similar to that which obtains in women with functioning ovaries. The advanced ageing of the individual apparently does not interfere with the capacity of the epithelial elements of the genital tract to respond in a physiologic manner to estrogens. We have, therefore, available in the estrogens, a group of substances that are powerful growth stimulators and that are capable of inducing intense proliferative activity in the vaginal and uterine mucosa as late as forty years after the cessation of normal ovarian function. In previous communications^{1, 2} we have reported our failure to find any evidence of abnormal proliferation in the genital tract of women following estrogen therapy. Because of the widespread therapeutic use of estrogens, particularly in women who fall into the age group in which carcinoma has its highest incidence, we felt it important to submit this problem to further study to determine whether the prolonged administration of estrogens may not result in excessive or abnormal endometrial or vaginal epithelial proliferation, leading possibly to neoplasia.

*Presented before the Third International Cancer Congress, Atlantic City, N. J., September 13, 1939.

MATERIAL

Our studies were conducted on a series of 206 women who have been treated with estrogens over periods varying from six months to five and one-half years and in whom vaginal and endometrial biopsies were performed during varying stages of the period of treatment.

The ages of the patients varied from 25 to 80 years, the majority being over 40 years of age. The patients were being treated for menopausal symptoms, functional amenorrhea, senile vaginitis, and kraurosis vulvae.

The estrogens were administered intramuscularly, in solution in oil (estradiol benzoate, progynon-B*; estradiol dipropionate, di-ovocylint), by mouth (estradiol, progynon-DH*), by vaginal suppositories (estradiol), by inunction (estradiol) and, during the past year, by implantation of pellets and crystals (estradiol, estradiol benzoate, and estradiol dipropionate). The hormones were administered in individual doses varying from 10,000 I.U. to 150,000 I.U. The total amount given varied from 500,000 I.U. to 23,400,000 I.U.

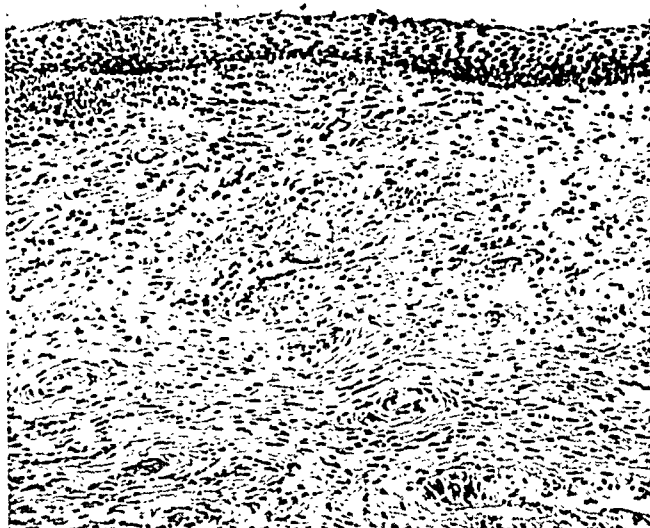


Fig. 1.—Case E. V., aged 52 years, spontaneous cessation of menstruation four years previously. Atrophic vaginal mucosa before treatment, indicating estrogen deficiency.

RESULTS

Effect of Estrogens Upon the Atrophic Mucosa.—The first noticeable effect of estrogen therapy upon the atrophic vaginal mucosa is a rapid proliferation of the basilar epithelial cells. This is discernible as early as four days after the intramuscular administration of as little as 100,000 I.U. (total) of estrogens. Proliferation proceeds at a rapid pace, leading to an increase in the number of epithelial layers and resulting in desquamation of some of the superficial epithelial cells. The proliferative activity is, however, not uniform, areas of hypoplasia being found adjacent to areas of active proliferation. This explains the finding of large, squamous, epithelial cells scattered among the atrophic cells

*For the estradiol benzoate (progynon-B) and estradiol (progynon-DH) used in this investigation, we are indebted to Dr. Erwin Schwenk, of the Schering Corporation, Bloomfield, N. J.

†For the estradiol dipropionate (di-ovocylin), we are indebted to Mr. Robert C. Mautner, of Ciba Pharmaceutical Products, Summit, N. J.

in the vaginal smears taken at this stage. If the estrogen administration is continued, there is a progressive increase in the number of epithelial layers, accompanied by an active process of desquamation. The latter is manifested by the appearance of a thick, white, vaginal secretion which consists almost entirely of desquamated, large, squamous, epithelial

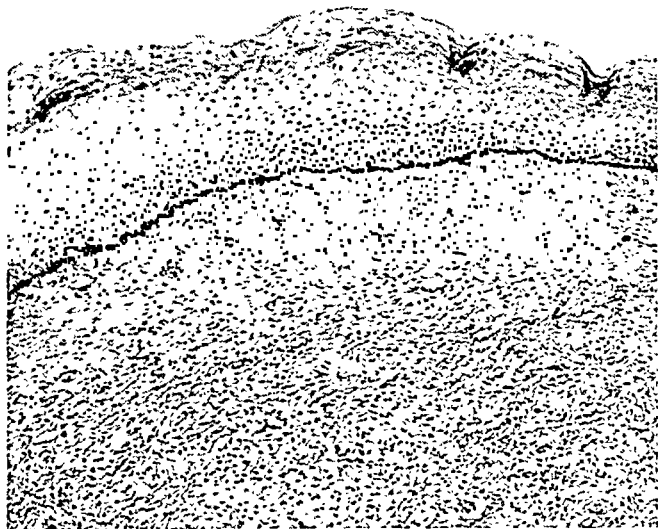


Fig. 2.—Vaginal mucosa showing incomplete regeneration after 600,000 I.U. of estradiol benzoate given during two weeks.

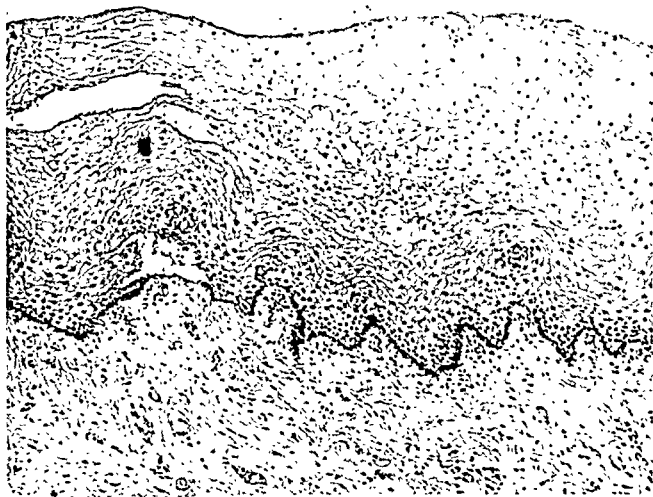


Fig. 3.—Vaginal biopsy nine weeks later (after 2,870,000 I.U. of estradiol benzoate) showing advanced proliferation.

cells. This degree of proliferation is attained with doses varying from 200,000 to 2,000,000 I.U. of estradiol benzoate administered intramuscularly. There is an amazingly wide variation in the individual response to equal amounts of the hormone. This variation in the proliferative response is probably due to a combination of factors, viz., the degree and duration of estrogen deprivation prior to the institution of estrogen

therapy, the rate of absorption, and the rate of excretion of the hormone. In some cases, doses of more than 2,000,000 I.U. failed to induce complete morphologic restitution. It is interesting to note that once morphologic restitution has been attained further increase in the dosage does not appear to produce any further progress in the proliferative response. Actually, in a number of cases, the vaginal mucosa appeared to be less

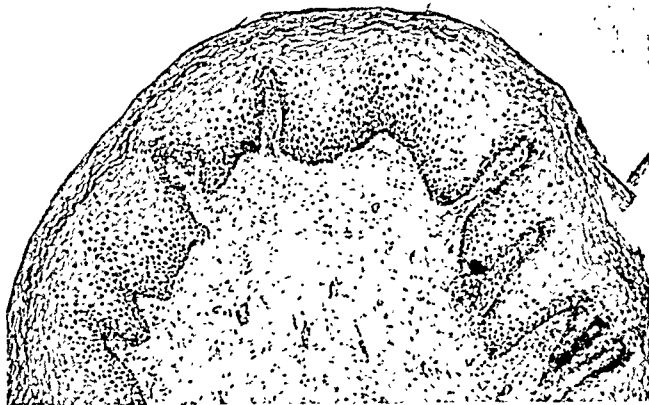


Fig. 4.—Vaginal biopsy after 20,200,000 I.U. of estradiol benzoate. Note absence of excessive or abnormal epithelial proliferation.

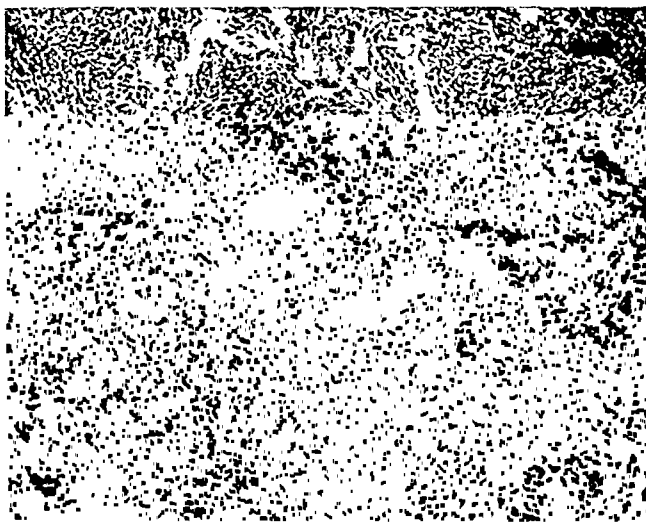


Fig. 5.—Case E. V.; preliminary endometrial biopsy showing atrophy of the endometrium, indicative of estrogen deficiency.

regenerated after the patient had received the larger doses than after the smaller ones. Compare Fig. 3 (showing vaginal mucous membrane after 2,870,000 I.U. of estradiol benzoate) with Fig. 4 (biopsy taken from the same patient after a total of 20,200,000 I.U. of the hormone was given). It is extremely significant that continuing the estrogen administration to this enormous dose did not produce any signs indicating excessive or abnormal proliferation.

Effect of Estrogens on the Endometrium.—The atrophic endometrium (Fig. 5) responds more slowly than the vaginal mucosa to estrogen stimulation. Not infrequently, amounts of estrogens (400,000 to 600,000 I.U.) that produce striking epithelial growth in the vaginal mucosa will result in only slight proliferation in scattered areas in the endometrium. As

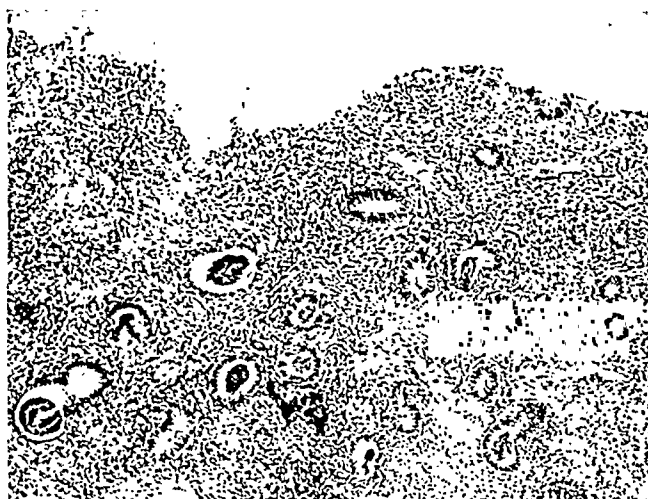


Fig. 6.—Endometrium after total of 1,200,000 I.U. of estradiol benzoate in four weeks, revealing proliferative pattern.

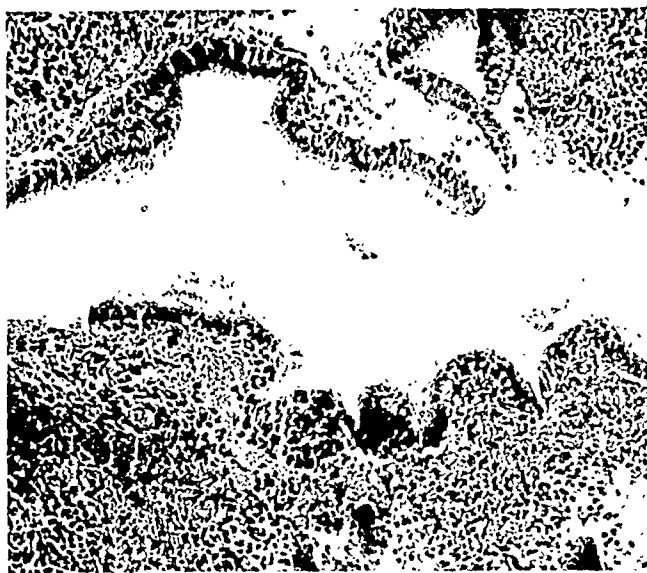


Fig. 7.—Endometrial biopsy taken during period of estrogen-induced bleeding. Patient had been bleeding for three days when this biopsy was obtained. Total dosage at this time was 1,500,000 I.U. of estradiol benzoate. Bleeding continued for four more days. Estrogens were not administered during the period of bleeding.

the dosage is increased, approaching the 1,000,000 I.U. level, the endometrium shows a more definite and more uniform proliferative response, resembling the normal proliferative pattern found in the normal post-menstrual phase of the cycle (Fig. 6). Uterine bleeding usually occurs after the patient has received approximately 1,000,000 to 1,500,000 I.U.

during four to six weeks. At this stage the endometrium is found to exhibit signs of active proliferation with some evidence of gland distention. Examination of the uterine blood in several cases has revealed



Fig. 8.—Endometrial biopsy taken four days after cessation of estrogen-induced bleeding and before the re-instatement of estrogen therapy. The biopsy reveals the endometrium to have regressed to a state of inactivity resembling the pre-treatment status.

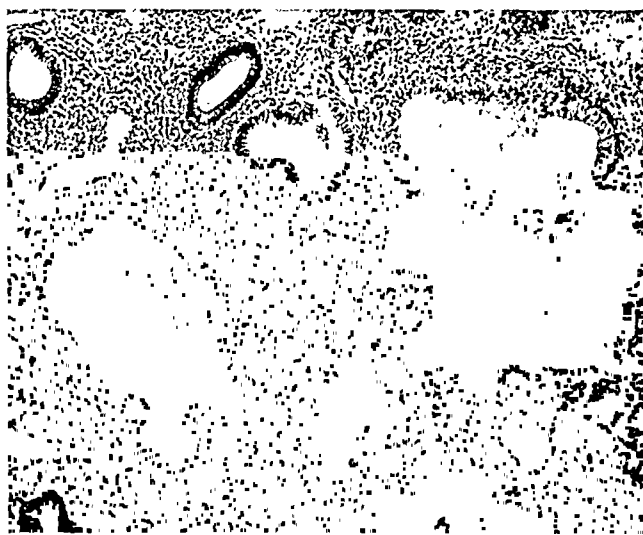


Fig. 9.—Case H. S., aged 55 years, menopause five years previously. Endometrial biopsy after a total of 18,500,000 I.U. of estradiol benzoate, administered during a period of thirty-four months. The endometrium is in a state of active proliferation with some cystic glandular dilatation. Estrogens were then stopped; uterine bleeding began six days later and lasted for five days.

desquamated fragments of endometrium containing glands and stromal cells. Biopsies performed during the period of bleeding exhibited various stages of proliferation associated with distended (cystic) glands.

Biopsies performed after the cessation of bleeding usually revealed a *quiescent* and, in many cases, an *atrophic endometrium*. Continued administration of estrogens after the uterine bleeding had ceased resulted in a repetition of the same proliferative process, followed by desquamation and bleeding and a return of the endometrium to its quiescent state. In some cases, this cyclical bleeding occurred at intervals of four to ten weeks for many months (six to thirty-eight months). It is noteworthy that in these cases the endometrium at the end of these long periods of estrogen stimulation, punctuated by recurrent episodes of bleeding, does not reveal any greater proliferative activity than after the initial course of estrogen stimulation.

Similar morphologic studies performed with estradiol dipropionate administered intramuscularly, estradiol administered orally, by skin inunctions, and by vaginal suppositories revealed essentially similar results.

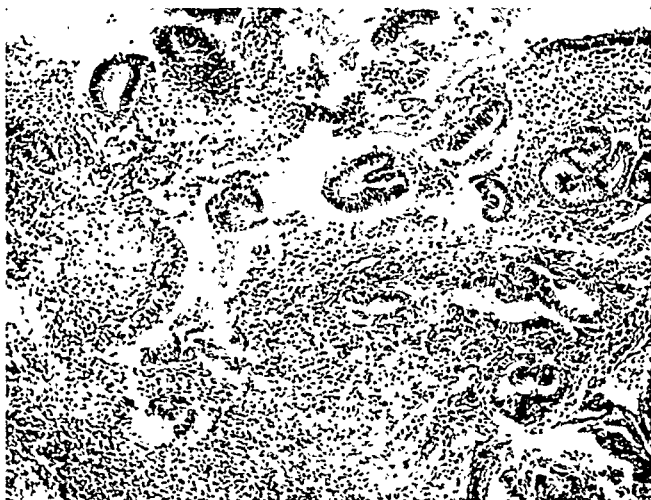


Fig. 10.—Endometrial biopsy taken ten days after the termination of the bleeding episode. The endometrium is in a quiescent, almost atrophic, state.

SUMMARY AND CONCLUSIONS

1. The administration of estrogens to women suffering from an estrogen deficiency results in regenerative changes in both the vaginal and uterine mucosa.
2. If estrogens are administered continuously, in adequate therapeutic doses, the vaginal mucosa responds with an orderly progressive regeneration of the epithelial layers, resembling the histologic pattern of the adult cyclical female with normal estrogen production.
3. Continued administration of estrogens leads to increased desquamation of the superficial epithelial layers without producing any signs of excessive or abnormal epithelial proliferation.
4. The atrophic endometrium responds to adequate estrogen therapy with an orderly regeneration of the epithelial, glandular, and stromal elements. Continued administration of estrogens (at the rate of approximately 1,500,000 I.U. per month) usually results in the appearance

of cystic glands, in some cases resembling the Swiss cheese pattern, associated with active proliferation of the stroma. In no case was any evidence of abnormal proliferation noted.

5. The same process of endometrial growth, desquamation (associated with bleeding) and regression, followed by regeneration, can be reproduced cyclically by repeating the course of estrogens.

6. It is obviously impossible in human beings to administer the huge doses of estrogens over the long periods of time that would justify comparison with the experimental production of carcinoma in rodents. However, the conclusion seems warranted, on the basis of these studies that, within the limits of the dosage used in this investigation (up to 53,400,000 I.U.), there appears no evidence to justify the fear that carcinoma of the genital tract may result from the therapeutic use of estrogens.

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THE PULSE AND RESPIRATORY VARIATIONS IN NORMAL WOMEN DURING LABOR*

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SINCE it has been suggested that the variations of the pulse and respiratory rate during labor would afford a warning of the approach of serious cardiac insufficiency in patients with heart disease,¹ it seemed important to determine the character of the variations in normal women. Such studies have not been found in the literature although recent work has touched upon many other phases of the cardiorespiratory reactions of pregnancy and labor. This recent work has been in relation to the prelabor period. Few investigations have been concerned with labor itself.

Martin² found that the pulse increased with the pains and returned to normal between pains during early labor but later, when the pains became more severe, he found that the pulse remained elevated. Probyn-Williams, and Cutler³ found the average pulse rate during labor to be 89. Gewurz⁴ noted a lability of the pulse during labor with stability during the puerperium. He also observed an increase of the pulse rate during labor with gradual decline in the puerperium. Hamilton⁵ stated that from the time the patient enters the hospital until she is delivered and is returned to her room, the pulse rate should be 100 or less, and any elevation over that value is due to insult: either medical, surgical, or obstetric.

The subject of post-partum bradycardia has received considerable attention, particularly during the second half of the last century. Its

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existence has been denied by some authors while others found it in 90 per cent of the patients. The majority reported an incidence greater than 20 per cent. The onset of the bradycardia is reported variously at from two hours to nine days post partum, and its duration at from several days to several weeks. Multiparas are said to show more slowing of the pulse than primiparas. Few authors have compared figures on the same patients before and after delivery. Heart block might be suspected from some of the extremely low rates reported, for they are in the zone that would suggest this condition.

Respirations were noted by Gewurz⁴ to be usually normal during labor and followed by a respiratory arrhythmia with onset shortly after delivery, and lasting for about nine days.

The present study was undertaken in an attempt to establish the normal behavior of the pulse and respirations during labor, and to evaluate, if possible, the influence of such related factors as total duration of labor, duration of the second stage, and analgesia. A similar study in cardiac patients is under way.

Although no definite routine of analgesia is followed in the New York Lying-in Hospital, the following may be given as the most common sequence.

In early labor if the pains are not unduly troublesome, analgesia is delayed until the cervix is found to be 4 or 5 cm. dilated, and the pains become more severe. At this time morphine and scopolamine are administered (morphine 0.010 Gm. and scopolamine 0.0004 Gm.). If labor progresses satisfactorily no further analgesia may be used. Occasionally, if pains are very severe and delivery seems reasonably remote, another dose of morphine may be given, or when the cervix reaches 7 cm. dilatation, rectal instillation of an ether, oil, and quinine mixture is given (75 c.c. ether, 2.6 c.c. alcohol, and 0.6, or 1.2 Gm. of quinine). In not a few instances, particularly in patients entering the hospital late in labor without having suffered unduly, no analgesia may be used, or possibly only rectal instillation of the mixture described above. After full cervical dilatation, patients receive nitrous oxide and oxygen during contractions and bearing down is encouraged until sufficient amount of the presenting part is visible to permit delivery. At this time ether is added to the mixture of gases.

RESULTS

One hundred and eighty patients were studied: 153 primiparas and 27 multiparas. The pulse and respirations were recorded by graduate nurses every fifteen minutes from the time of admission in labor until delivery, and thereafter on the wards every four hours. A chart was made of each case similar to those of Figs. 1 to 5 and from a study of these charts the following data were obtained. It was found unsatisfactory for the purposes of summary to consider each separate pulse and respiratory count because certain figures were only reached once or twice, and the differences between successive counts were often considerable and at times alternately up and down as shown by the pulse counts in the central portion of Fig. 5. For this reason each chart was summarized by considering the average level of the pulse and respirations for 3 or 4 successive counts, the pulse level being considered to the nearest multiple of 10 and the respiratory level to the nearest even number. Isolated aberrant counts were disregarded such as the two respiratory counts of 38 seen in Fig. 5. This chart was summarized as the pulse reaching 140 and the respirations 28 per minute. Of the 180 patients studied, only 10 (5 per cent) showed an increase in pulse rate of more than 20 per minute. Of the remaining 170 patients, 87, or about half, failed to show any change in the pulse during

labor. Of the total patients studied, 17 (9 per cent) showed an increase in respirations of more than 8 per minute. Of the remaining 163 patients, 75, or slightly less than one-half, showed no change in respirations during the course of labor. Fifty-six patients (31 per cent) showed no change in either pulse or respirations during labor.

Because some patients appeared first with a slightly elevated pulse, such as 85 or 90, it seemed better to consider the maximum pulse rate and respiratory rate which was reached and maintained for the duration of three consecutive counts. On this basis it was found that in 41 patients (23 per cent) the pulse rose to above 110 or the respirations to above 24 per minute. In 18 patients (10 per cent) the pulse rose above 110 per minute, and in 34 patients (19 per cent) the respirations rose above 24 per minute. There were 12 patients (7 per cent) having both the maximum pulse above 110 and respirations above 24 per minute. All of the 10 patients with pulse increasing more than 20 per minute were in the group with pulse rising above 110 or respirations above 24 per minute. Fifteen of the 17 patients with respirations increasing more than 8 per minute fell in the same groups.

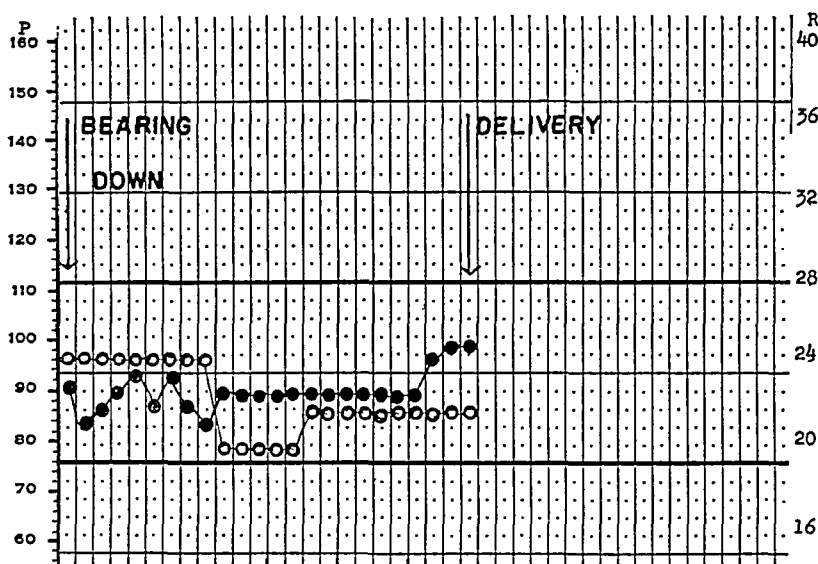


Fig. 1.—Pulse and respirations in the latter part of labor. Primigravida. Total labor 81 hours. Recordings every 15 minutes. Practically no change in pulse or respirations throughout entire labor. ○ respirations; ● pulse.

Of the patients with the pulse rising above 110: 7 reached 120 (respiration counts from 24 to 28); 7 reached 130 (respiration counts from 20 to 40); and 4 reached 140 (respiration counts of from 28 to 32). Of the patients with respirations rising above 24 per minute: 2 reached 26 (pulse counts of 90); 12 reached 28 (pulse counts from 80 to 140); 4 reached 30 (pulse counts from 80 to 140); 12 reached 32 (pulse counts from 90 to 140); and 4 reached 40 (pulse counts from 80 to 130). Neither intrapartum lability of pulse, nor post-partum bradycardia, nor post-partum respiratory arrhythmia was observed.

Table I illustrates graphically certain of the above features, while Table II shows the frequency of the various combinations of different degrees of pulse and respiratory disturbance. Figs. 1 to 5 are copies of actual charts illustrating certain frequent types of reaction. Fig. 1 shows the chart of the last six hours of a long labor. The respirations were 24 per minute at first but later fell to 20 after the administration of morphine and then rose to 22 at the end. Fig. 2 shows the chart of the last nine hours of a twenty-seven-hour labor. The pulse remained in the neighborhood of 80 for most of the time but at the end rose to 84. The respirations remained at 18 until the second stage when they rose gradually to 22. Fig. 3 is the chart of the last 5.5 hours of a 16.5 hour labor. During the earlier

part of the labor the pulse remained at about 80 and the respirations at 22. The pulse rose to 84 and 86 just before the second stage and the respirations remained at 20 only to suddenly rise to 39 at the onset of the second stage. Reactions of this sort are relatively uncommon, occurring in only 8 cases of the series (4.5 per cent) and generally are observed in women of a nervous or neurotic type. Fig. 4 shows the last seven and one-half hours of a twenty-five-hour labor. The pulse had remained at about 90 and the respirations at 20 before this portion of the chart was reached. At about the beginning of the second stage the pulse rose to about 120 at which level it remained and the respirations rose more gradually to a maximum of 24 and then gradually fell to 22. This is a moderately severe reaction which had it been observed in a cardiac patient might have occasioned some alarm. Fig. 5 is a record of the last nine hours of a fifty-two-hour labor. Previous to this

TABLE I. BEHAVIOR OF PULSE AND RESPIRATIONS DURING LABOR IN
180 NORMAL WOMEN

<i>Cases</i>	<i>Pulse</i>		
4 reached 140 (resp.: 28, 28, 30, 32)			
7 reached 130 (resp.: 20, 24, 28, 32, 36, 40, 40)			
7 reached 120 (resp.: 24, 24, 24, 24, 24, 24, 28)			
Pulse over 110 per minute 18, or 10%			
Pulse unchanged 87, or 51%			
		No change either pulse or resp. 56 or 31%	Pulse over 110 and resp. over 24 12 or 7%
Respirations unchanged 75, or 42%			
Respirations over 24 per minute 34, or 19%			
<i>Cases</i>	<i>Resp.</i>		
2 reached 26 (pulse: 90, 90)			
12 reached 28 (pulse: 80, 80, 94, 100, 100, 100, 100, 110, 120, 130, 140, 140)			
4 reached 30 (pulse: 80, 90, 130, 140)			
12 reached 32 (pulse: 90, 90, 90, 90, 90, 90, 90, 90, 100, 110, 130, 140)			
4 reached 40 (pulse: 80, 100, 130, 130)			

In the upper section of this table is given the maximum respiratory rate of each individual with a pulse over 110. The number of patients with a pulse of 120, 130, and 140 is indicated, and the respiratory rates in the individual patients of each group. Similarly the lower section shows the patients with maximum respiratory rates over 24 and the maximum pulse rates in the individual patients of each grade of respiratory increase.

TABLE II. THE PERCENTAGE DISTRIBUTION OF VARIOUS TYPES OF PULSE AND
RESPIRATORY REACTIONS

No change in either pulse or respiratory rates (56 cases)	31%
Mild reactions:	
No change in pulse rate, respiratory rate increased but did not exceed 24 (2 cases)	1%
No change in respiratory rate, pulse rate increased but did not exceed 110 (2 cases)	1%
Moderate reactions:	
Pulse and respiratory rates both increased but pulse rate did not exceed 110, nor respiratory rate exceed 24 (76 cases)	43%
No change in pulse rate, respiratory rate exceeded 24 (24 cases)	13%
No change in respiratory rate, pulse rate exceeded 110 (20 cases)	4%
Marked reactions:	
Pulse rate exceeded 110 and respiratory rate exceeded 24 (12 cases)	7%

portion of the chart the pulse had been fairly level at about 100 and the respirations at 20. Two and one-half hours before the second stage the pulse began to rise, eventually reaching 120 but the respirations remained at 20 until the bearing down began, when the pulse promptly rose to 140 and the respirations to 28. These

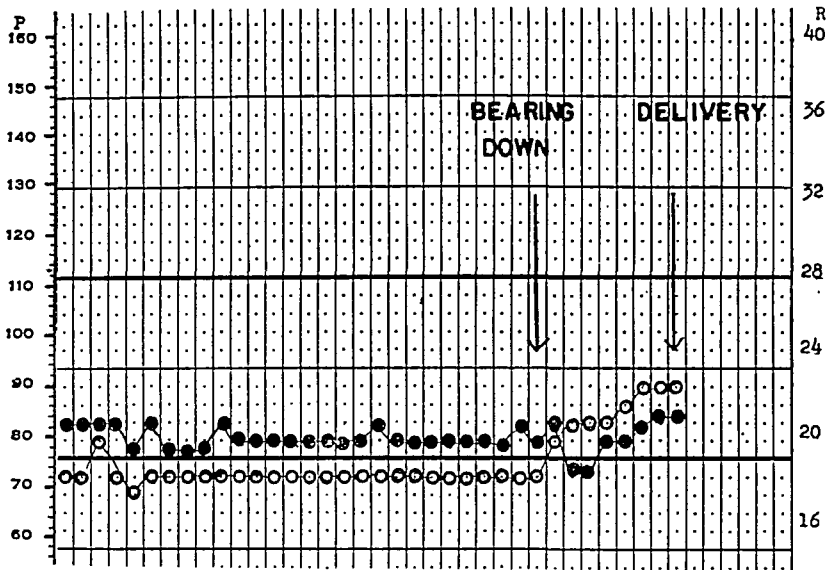


Fig. 2.—Pulse and respirations in the latter part of labor. Primigravida. Total labor 27½ hours. Recordings every 15 minutes. Small increase in respiratory rate and no change in pulse rate, pulse having remained at 80 and respirations at 18 throughout earlier part of labor. ○ respirations; ● pulse.

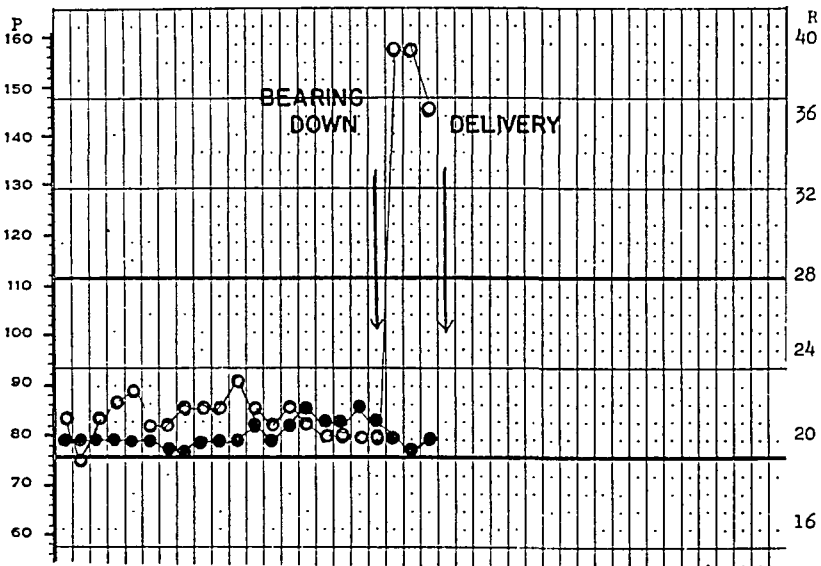


Fig. 3.—Pulse and respirations in the latter part of labor. Multigravida. Total labor 16½ hours. Recordings every 15 minutes. Large increase in respiratory rate without change in pulse rate, pulse having remained at 80 and respirations at 22 throughout earlier part of labor. ○ respirations; ● pulse.

levels were approximately maintained for three hours until delivery, after which the pulse and respirations fell to normal levels in eight hours. Had this picture appeared in a cardiac patient it would so strongly have suggested cardiac strain that in all probability labor would have been accelerated by appropriate means. It is of greatest importance to appreciate that such severe cardiorespiratory reactions may

appear in healthy women and noteworthy that they appeared only during the second stage.

In order to find some explanation of this phenomenon which appears in 7 per cent of our patients, we have considered various possibilities. Anemia can be

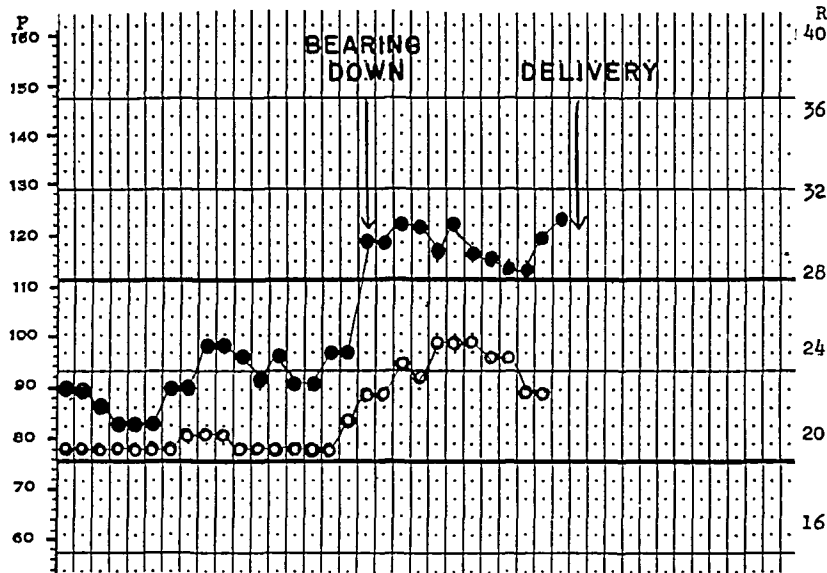


Fig. 4.—Pulse and respirations in the latter part of labor. Primigravida. Total labor 25 hours. Recordings every 15 minutes. Small increase in respiratory rate and large increase in pulse rate, pulse having remained at 90 and respirations at 20 throughout earlier part of labor. ○ respirations; ● pulse.

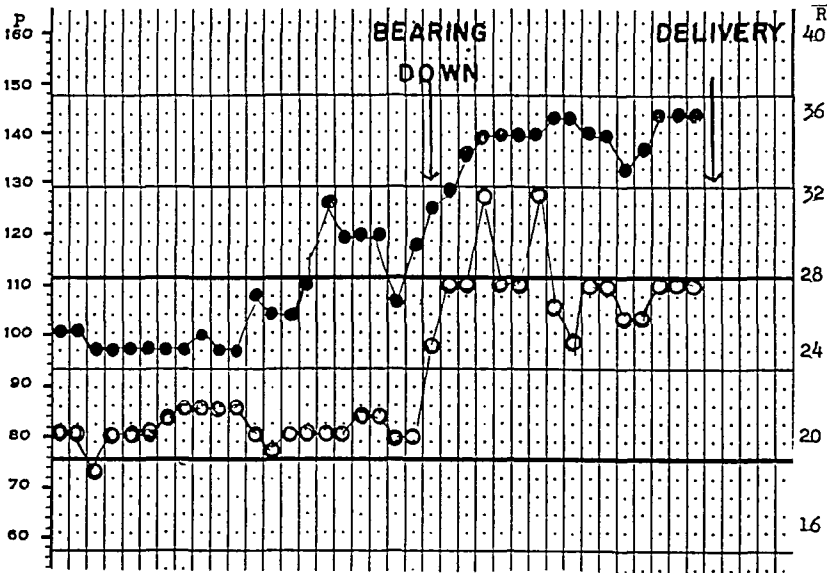


Fig. 5.—Pulse and respirations in the latter part of labor. Primigravida. Total labor 52 hours. Recordings every 15 minutes. Graph showing terminal increase in pulse and respiratory rates, pulse having been at 100 and respirations at 20 throughout earlier part of labor. ○ respirations; ● pulse.

ruled out, as none of the patients in this group was anemic nor had any other medical complication. It was observed that during labor pains there was usually a slight increase of pulse rate and a slight decrease of respiratory rate. When the contractions had subsided there was a return to the former levels. It was observed also as can be seen in the figures that when a persistent increase of pulse or respira-

tions was present, it almost always began with the second stage of labor or shortly before.

To determine whether these pulse and respiratory changes might have been affected by analgesia or by the total duration of labor or by the duration of the second stage, an analysis was made as shown in Table III.

Because of the possibility that some of the pulse and respiration values may have been influenced by drugs, it is worth while to consider briefly the action of such drugs as the patient may have received.

Morphine is a central respiratory depressant. By virtue of its action on the vagus nerve it also causes slowing of the heart. Pain is an antidote for morphine, however, and can in part nullify its effects. Scopolamine paralyzes the vagal endings and accordingly tends to counteract the effects of morphine. Rectal ether initially tends to produce respiratory irregularity. Ultimately the respirations are slowed and become regular. When a combination of the above drugs is used, their varied

TABLE III

<i>Pulse Rising Over 110 or Respirations Rising Over 24</i>								
	EITHER		PULSE		RESPIRATIONS		BOTH	
	PATIENTS	%	PATIENTS	%	PATIENTS	%	PATIENTS	%
	41	23	18	10	34	19	12	7
Analgesia								
62 none*	15	24	7	11	13	21	4	6
32 ms, re	8	25	3	10	7	22	3	10
42 ms	7	17	4	10	8	21	3	7
29 re	11	37	4	13	6	21	2	6
Total labor over 30 hr. 46 patients 26%	18	39	8	17	15	33	5	11
Total labor 30 hr. or less 134 patients 74%	23	17	10	7	20	14	7	5
Second stage over 2 hr. 56 patients 31%	14	25	5	8	14	25	5	9
Second stage 2 hr. or less 124 patients 69%	27	21	13	10	21	16	7	6

No Change in Pulse or Respirations

	BOTH		PULSE		RESPIRATIONS	
	PATIENTS	%	PATIENTS	%	PATIENTS	%
	56	31	87	51	75	42
Analgesia						
62 none*	23	37	33	53	30	48
32 ms, re	11	34	17	53	12	37
42 ms	13	30	22	52	19	45
29 re	9	31	15	51	14	48
Total labor over 30 hr.	10	21	18	38	14	30
Total labor 30 hr. or less	46	34	69	51	61	45
Second stage over 2 hr.	10	18	15	26	11	19
Second stage 2 hr. or less	46	37	72	58	64	51

*None, no analgesia; ms, morphine and scopolamine; re, rectal ether.

actions scarcely allow one to predict the net result upon pulse or respirations.

A study of Table III fails to show any correlation between analgesia and pulse or respirations during labor. In comparing the groups which did and did not receive analgesia, one is unable to find a significant difference in the pulse or respiration values. Nor do the values with any one type of analgesia seem to differ from those with any other.

The data of Table III indicate, however, that both an increase in the total duration of labor and also in the duration of the second stage, tend to produce a rise in the pulse and respiration values. This increase generally, as has been said, occurs at the time of the second stage or shortly before. Some patients experience the urge to push with the contractions before full cervical dilatation is reached and actually, if a rise in pulse and respirations is to occur, it starts with the appearance of bearing-down efforts, and the initial rise begins within the first half hour of such effort.

There were, however, several instances of prolonged labor during which the pulse and respirations failed to rise significantly or at all. In all cases of prolonged labor, maternal exhaustion and acidosis were treated by oral and parenteral administration of glucose and fluids, and it is believed that without this type of obstetric care more of these patients might have shown an elevation of pulse and respirations.

It is of interest that 8 of the 18 patients with the pulse rising over 110 showed persistence of tachycardia throughout the puerperium, although there were no instances of anemia, puerperal hemorrhage, infection, thyroid, or cardiorespiratory disease. Post-partum tachycardia was only found in patients who had shown a rise of pulse rate to over 110 during labor. In some patients abdominal, rectal, or vaginal examination was observed to be sufficient to significantly raise the pulse for a short period. This suggests that anxiety might have been the factor in the rapid heart rate of these patients and possibly also in those with persistent post-partum tachycardia. Although post-partum bradycardia was not observed, it would seem reasonable to explain relative slowing of the pulse on the basis of the bed rest incident to the early puerperium.

Only one patient had a respiratory rate over 20 during the first day post partum. She had shown an increased respiratory rate during labor. She was a primipara and had a labor of nineteen hours' total duration, being forty-eight minutes in the second stage. Before the second stage, her pulse had varied from 80 to 90 and her respirations from 22 to 24. About three-quarters of an hour before the second stage her pulse and respirations began to rise gradually and during the second stage her pulse reached 110 and her respirations, 28. The general picture of this woman's chart resembled rather closely that of Fig. 5. The first day post partum her respirations varied from 24 to 22, on the second day they varied from 22 to 20, and thereafter they were 20 or less. The pulse post partum was over 100 once or twice each day for the first 4 or 5 days. No pelvic complication was discovered. There were no pulmonary râles.

CONCLUSIONS

In normal women during labor the pulse and respirations usually change but little until voluntary bearing-down efforts are brought into play. This occurs at or shortly before full dilatation of the cervix. There is a short insignificant increase in the pulse and decrease in the respirations during contractions with return to former levels during the intervals.

With the onset of bearing-down efforts the pulse, or respirations, or both may remain unchanged or may increase. The pulse seldom increases more than 20 beats per minute but exceeds 110 per minute in 10 per cent of the cases. Respirations seldom increase more than 8 per minute but exceed 24 per minute in 19 per cent of the cases. It is unusual for both pulse and respirations to exceed these values, this occurring in only 7 per cent of the cases.

No correlation could be found between the level of pulse or respirations and either the use of analgesia or the particular analgesic used.

Prolonged labor and prolonged second stage increase the liability to acceleration of pulse and respirations.

Other than a transient rise during labor pains, liability of pulse during labor was not prominent. Post-partum bradycardia and post-partum respiratory arrhythmia were not observed.

Relative slowing of the pulse post partum is not out of proportion to the bed rest incident to that period.

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RHEUMATIC HEART DISEASE IN PREGNANCY

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PREGNANCY complicated by rheumatic heart disease has been the subject of a recent study at the Margaret Hague Maternity Hospital. A total of 345 cases were reviewed, dating from 1933 to 1939. All cases, private, clinic, and "neglected," were included. By the neglected case we mean to designate the pregnant woman who, without previous medical attention, was first seen by us in cardiac failure. The incidence of heart disease at this hospital for the years studied was 1.2 per cent, based on total admissions. This figure falls within the range reported by kindred institutions in this country. Rheumatic heart disease made up 95 per cent of all cases of heart disease.

By and large it can be said that the treatment of heart disease once present resolves itself into the effort to prevent decompensation. In the pregnant woman with heart disease, the occurrence of heart failure is of vital importance. Because of this self-evident fact every effort should be made to prevent this complication. We feel it possible to foretell fairly accurately which patient will decompensate when burdened with a pregnancy if the deleterious effects of this burden are not counteracted by bed rest. Three extremely important prognostic aids appeared in the analysis of our cases. All three are contained in the patient's history, (1) the functional cardiac capacity prior to pregnancy, (2) the patient's age, and (3) the presence or absence of previous cardiac failure.

We followed the New York Heart Association classification, as follows:

- Class 1: Patients with cardiac disease and no limitation of physical activity.
- Class 2A: Patients with cardiac disease and slight limitation of physical activity.
- Class 2B: Patients with cardiac disease and marked limitation of physical activity.
- Class 3: Patients with cardiac disease who are unable to carry on any physical activity without discomfort.

Of 345 patients with rheumatic heart disease seen since 1933, 77 decompensated, an incidence of 22.3 per cent. Table I shows the incidence of cardiac failure in relation to the functional classification.

TABLE I. CARDIAC FAILURE IN RELATION TO FUNCTIONAL CLASSIFICATION

CLASS	TOTAL	FAILED
I	143	4 — 2.8%
2A	116	9 — 7.7%
2B	81	59 — 72.8%
3	5	5 — 100%
	345	77 22.3%

Thus the incidence of failure in pregnancy quite naturally increases as the functional capacity in the nonpregnant state decreases. The burden of pregnancy can be borne without serious difficulty by the comparatively well-functioning hearts, while the same burden will cause decompensation in the badly incapacitated group.

Additional prognostic information is obtained from the age of the patient. We have divided our patients into five-year age groups ranging from fifteen to over forty, and determined the incidence of decompensation in each group (Table II).

TABLE II. CARDIAC FAILURE IN RELATION TO AGE

YEARS	TOTAL	FAILED
Less than 20	32	4 — 12.5%
21-25	135	13 — 9.6%
26-30	100	26 — 26.0%
31-35	49	16 — 32.6%
36-40	25	14 — 56.0%
More than 40	4	4 — 100%
	345	77 22.3%

In general, it may be said that the older the cardiac patient the greater the possibility of a breakdown occurring in the pregnant state. The minor discrepancy shown in the less-than-twenty group is possibly due to the relatively small number in this class. To make the association between age and incidence of decompensation more striking, the patients may be divided into two groups, those less than thirty and those more than thirty years of age. The failure rate in the younger group was 16.1 per cent, compared to 43.6 per cent in the older group. It should be added that the patient's age and the functional capacity of her heart are certainly dependent to some extent upon one another. In our series the older groups very naturally contained the higher percentages of functionally bad hearts.

What a pathologic heart will do when forced to support a pregnancy may to some extent be foretold by its previous record. Did the patient ever decompensate before? In our series there were 11 patients who had decompensated previously but did not compensate in the pregnancy under consideration. Thirty-three patients gave a history of cardiac failure in the past and decompensated again in the pregnant state.

Thus, of 44 women who suffered broken compensation previously, 75 per cent decompensated again when pregnancy complicated the heart disease. If a patient has never decompensated before, her chances of cardiac failure when the burden of pregnancy is assumed are 14.1 per cent.

TABLE III. PROGNOSTIC VALUE OF HISTORY OF DECOMPENSATION

Cardiac failure previously <i>but not</i> in this pregnancy	11
Cardiac failure previously <i>and again</i> in this pregnancy	33
Cardiac failure for the <i>first time</i> in this pregnancy	44
Previous cardiac failures	44
Previous cardiac failures and again in this pregnancy	33 — 75%

A similar association was reported in 1926 by G. H. Hunt.¹ In his series of 156 cases, 50 per cent of the previous cardiac failures decompensated again, as compared to a 17 per cent cardiac failure rate in pregnancy when no decompensation had occurred before. His total failure rate of 21 per cent matches very closely the 22.3 per cent in our group and the 19.2 per cent reported by the Boston Lying-in Hospital.

We feel certain that attention to these prognostic signs has helped us immeasurably in our handling of the pregnant woman with heart disease. In the last 103 consecutive cardiac patients delivered at the Margaret Hague Maternity Hospital (these are not included in the above statistics), there have occurred two failures, one of which was probably preventable, an incidence of less than 2 per cent. This was accomplished by careful prenatal observations at frequent intervals, by the prompt institution of absolute bed-rest at the first suspicion of any decrease in cardiac reserve, and, most important, by the hospitalization of any patient who presented a history of previous cardiac failure or a combination of prognostic signs that indicated the possibility of difficulty. It has been our experience that if the need for bed rest arises at any period in the pregnant state the rest must be absolute and continuous for the duration of the gestation.

Feeling satisfied that by the application of the principles mentioned above we have been able to decrease the decompensation rate among our pregnant women with rheumatic heart disease to an almost negligible incidence, we felt it was important to determine when in the pregnancy the patient might be expected to experience the most difficulty. Knowing at what time the burden of pregnancy exerts its maximum effect upon the heart would enable us to fortify our therapeutic attack with preventive measures. Before presenting the analysis of our patients with this view in mind, it is necessary to note that a fairly clear concept of the dynamics of the circulation of the normal pregnant woman has resulted from the laboratory and clinical work of several observers.² Much has been done in studying the circulatory burden in pregnancy, but only a few pertinent determinations will be mentioned here. Studies of the total blood volume have usually shown a progressive increase from the early months of pregnancy to a maximum in the eighth month. During the last month of pregnancy the blood volume decreases, from an average of 45 per cent above the normal

for the nonpregnant woman to reach normal two weeks post partum. Experimentally it has been shown that increased blood volume leads to increased cardiac output. Studies on the velocity of blood flow show a gradual increase during the course of pregnancy and a slowing up as the expected date of confinement approaches. Thus the cardiac load begins to increase when the pregnancy begins and progresses steadily to reach a maximum during the eighth month. In the last month of pregnancy, not at delivery but during a period of four to six weeks preceding it, the blood volume, the cardiac output, and the velocity of blood flow tend to return toward normal levels with a consequent diminution of cardiac work. Through such studies it has been possible to "see" the burden that the pregnancy places upon the heart, a burden carried by the normal heart with no, or at least little, difficulty. However, this seemingly extra load is sufficient to embarrass a previously damaged heart, unless other factors known to strain cardiac capacity are appreciated and strenuous attempts made to remove the "medically removable" burdens. We have attempted to correlate this physiologic concept with clinical experience.

Table IV shows when the failures in our series occurred.

TABLE IV. CARDIAC FAILURE IN PREGNANCY: TIME OF OCCURRENCE

TIME	NO.	PER CENT
1-6 mo.	40	51.9
7-8 mo.	22	28.5
9 mo.	8	10.3
Labor	5	6.4
Puerperium	2	2.5
	77	

Eighty per cent of the cardiac failures in this series were found to occur during the first eight months, with the greatest incidence concentrated in the seventh and eighth months. Thus, from a clinical standpoint, too, the cardiac difficulties begin when the pregnancy begins and reach a point of maximum intensity four to six weeks before term. Therapeutic measures, therefore, to avoid decompensation must be instituted in the beginning of pregnancy. The "medically removable" burdens must be rigidly controlled from the very start; increased bed rest should be ordered from the first month of gestation, and absolute bed rest enforced when any suspicion of decreased cardiac reserve appears.

Clinical confirmation of the lightening of the cardiac burden in the last four to six weeks of gestation, suggested by the physiologic changes, has been sought for in our hospitalized cases. We have been so impressed with the improvement shown by rheumatic cardiac patients during the last month of gestation that we now anticipate it. Rarely is anything more than absolute bed rest ordered, withholding digitalis wherever possible, so that a clear-cut picture of the physiologic lightening of the circulatory burden the last month may be clinically observed. To date, we have had no reason to regret this relative inactivity, while, as a matter of fact, we feel that several cases have resulted in successful terminations only because of the waiting period, thus allowing the

physiologic improvement to exert its full beneficial effect. Of the several examples available only two of the more serious grades of cardiac decompensation will be reviewed.

CASE 1.—L. D. (History 17836), aged 42 years, para v, gravida vi, had rheumatic heart disease with enlarged heart, mitral stenosis, and insufficiency, Class 2B. She was digitalized and followed as an outpatient for approximately one month. She was admitted to the hospital because of a progressively decreasing capacity in the seventh month, complaining of cough, palpitation, dyspnea, orthopnea, and edema. Examination revealed many coarse rales throughout both lung bases, and marked edema. She could not tolerate any position in bed other than a 70 to 80 degree elevation of the back rest. The exertion of speaking caused obviously increasing distress. Moving from the bed to a stretcher in the eighth month resulted in extreme dyspnea and cyanosis. However, with no important change in medical care aside from most rigidly controlled rest, this patient managed to survive. Improvement occurred to an observable degree during the last few days of February, 1939. On March 7, 1939, the average ventricular rate was 72; ankle and sacral edema had disappeared. On March 18, spontaneous labor began. After fifty-two hours of difficult labor, this patient was delivered by midforceps. Her course during labor was splendid from a cardiac standpoint, as her pulse never rose above 90. The patient was discharged in relatively good condition on Apr. 12, 1939.

CASE 2.—R. E. (History 277), aged 43 years, para x, gravida x, had rheumatic heart disease with enlarged heart, mitral stenosis, and insufficiency with auricular fibrillation. The past history revealed at least three known attacks of cardiac failure during the past year. In fact, the patient became pregnant only a short time following discharge from another hospital where she underwent treatment for the third decompensation. On admission, in the tenth week of her pregnancy, her condition was quite similar to the case above described, with dyspnea, orthopnea, generalized edema, cyanosis, and fibrillation. Patient was digitalized and well rested. Months afterwards, digitalization and bed rest having been maintained, a Thanksgiving Day program with dinner, visitors, etc., was apparently sufficient to cause a severe attack of pulmonary edema. After seven months of absolute bed rest and only during the last few weeks of her pregnancy did this patient begin to achieve some degree of compensation. Spontaneous labor began on Feb. 26, 1938, and a cesarean section was performed shortly afterwards. Her post-operative course was remarkably smooth from a cardiac standpoint. When she was discharged on Apr. 4, 1939, in fair condition, she was able to carry out only the lightest of exertions. Three months later a fatal attack of decompensation occurred.

Both patients reviewed had cardiac failure in the early months of pregnancy. Both were desperately ill until the last month of gestation. Both improved in the last four weeks to a clinically demonstrable degree without any change in the therapeutic regime, one sufficiently to withstand a long labor and the other a cesarean section. As an obvious corollary, it has appeared logical to us to take advantage of the lightening of the load in the last month, to allow the gestation to go to term and to avoid late pregnancy interference when the circulatory burden is at its height.

The labor experience brought to light by the analysis of this series has materially influenced the management of patients with cardiac disease. Decompensation occurred during labor in only five instances. A careful review of these five cases has forced us to correct the incidence of failure in labor to one case in 345 deliveries. The following brief case abstracts give our reasons for this correction.

CASE 3.—H. H. (History 25666), aged 26 years, para 0, gravida i, had rheumatic heart disease with enlarged heart, regular sinus rhythm, mitral insufficiency and stenosis, Class 1. Patient attended our ante-partum clinic, and by error was considered to have a normal heart. She was admitted to the hospital in labor at term. After five and one-half hours of labor she suddenly developed acute pulmonary edema and hemoptysis. The cardiac disease was then discovered. A blood count, however, done just before delivery showed 2.5 million red cells and 50 per cent hemoglobin, the smear revealing many microcytes.

Improper clinic diagnosis and a marked secondary anemia of the microcytic type must also be considered in attempting to appraise this failure.

CASE 4.—V. L. (History 30780), aged 28 years, para 0, gravida i, had rheumatic heart disease with enlarged heart, mitral insufficiency and stenosis, regular sinus rhythm, Class 1. Patient was seen in the ante-partum clinic for almost seven months. Her complaint of cough during all this time was not considered seriously. She was admitted in labor at term. After thirty-nine hours of labor and immediately following an infusion of 500 c.c. of 25 per cent glucose, she developed pulmonary edema and severe cough, the ventricular rate jumping to 120. Rapid digitalization and a bloodless phlebotomy brought improvement, allowing a vaginal operative delivery later without complication.

It is our feeling that this individual was showing some evidence of decompensation for seven months prior to delivery, explaining the chronic cough, and that the relatively large amount of hypertonic solution given intravenously was sufficient to cause an acute episode.

CASE 5.—H. S. (History 37168), aged 30, para 0, gravida i, rheumatic heart disease with enlarged heart, mitral insufficiency and stenosis, regular sinus rhythm, Class 1. This patient suddenly developed acute cardiac failure after twelve hours of an otherwise normal labor.

This undeniably was an acute failure in labor.

CASE 6.—E. G. (History 31302), aged 20 years, para 0, gravida i, had rheumatic heart disease with enlarged heart, mitral insufficiency and stenosis, regular sinus rhythm, Class 2B. Patient was under clinic care and was admitted three weeks before term for bed rest. After four hours of normal labor an occasional rale was noted at the lung bases and what was called a slow fibrillation was reported. Immediately following delivery the ventricular rhythm was normal and no rales were heard.

This patient was not seen by a cardiologist and the evidence for cardiac decompensation is meager.

CASE 7.—A. H. (History 9889), aged 35 years, para iii, gravida iv, had rheumatic heart disease with enlarged heart, mitral stenosis and insufficiency, regular sinus rhythm, Class 2B. Patient was seen in the clinic in early pregnancy. In the sixth month of her pregnancy she complained of dyspnea and orthopnea, requiring three pillows for sleep, and had frequent nose bleeds. Patient returned in the seventh month, complaining of severe abdominal pain and bleeding. During a labor induced by bagging on account of uterine bleeding (placenta previa), a rapid pulse and basilar rales were noted.

On the chart this patient is diagnosed as an acute cardiac failure in labor. We feel that it cannot be denied that this individual exhibited definite symptoms of markedly decreased cardiac reserve in the sixth month of her pregnancy, severe enough to be classed as decompensation; and second, it should be noted that induction of labor was compelled

by an obstetric complication in the seventh month, when her circulatory burden was about at its greatest load.

Thus, it is our opinion that only one of these five so-called failures in labor may actually belong in this classification; one failure in labor in 345 cases, an incidence that impresses us as being no higher than the accident rate in rheumatic heart disease. The individual who has had the benefit of careful prenatal observation with preventive measures taken as indicated should enter labor compensated, and the onset of decompensation during labor need not be feared.

This brings us to the final consideration in this report, the value of cesarean section in heart disease. We know of no satisfactory quantitative estimation of the amount of work done during labor and the possible resultant strain on the heart. We know of no good way to estimate the burden placed on a heart by cesarean section and the postoperative period. An attempt was made to judge the effects of a normal spontaneous labor as compared to the effects of a cesarean section. The inadequacies of the following figures in answering this problem are fully realized by the authors. We have compared the convalescent periods of twenty-four cesarean sections to that of 304 vaginal deliveries, an unequal comparison at best, but reflecting our tendency in management.

TABLE V. CONVALESCENCE: CESAREAN SECTION VS. VAGINAL DELIVERY

	CESAREAN SECTION	VAGINAL DELIVERY
Total	24	304
Fever more than 3 days	7 — 29.1%	13 — 4.2%
Pulse over 90 more than 3 days	21 — 87.5%	105 — 34.5%
Fever more than 5 days	5 — 20.8%	8 — 2.6%
Pulse over 90 more than 5 days	18 — 75.0%	59 — 19.4%

The post-partum period in women who have had a cesarean section is accompanied by elevated temperature and pulse readings much more often than in patients who have had a vaginal delivery. The possibility of vomiting, abdominal distention, and pain with their concomitant strain upon the heart must also be carefully appraised in judging the burden to the patient of a cesarean section compared to a vaginal delivery.

The mortality rates are compared in Table VI.

TABLE VI. MORTALITY: ABDOMINAL OPERATIVE DELIVERY VS. VAGINAL DELIVERY

	CESAREAN SECTION AND HYSTEROTOMIES	VAGINAL DELIVERY INCLUDING SPONTANEOUS ABORTIONS
Total	29	314
Deaths	4 — 13.8%	6 — 1.9%
Corrected	2 — 6.9%	4 — 1.2%

Four deaths occurred in the operative group, an incidence of 13.8 per cent. Two of these deaths may be discounted, one being sectioned at the moment of death in an attempt to save the fetus, the other only after the patient's condition was considered hopeless. Of 314 vaginal deliveries, including four spontaneous abortions, 6 died, a mortality of 1.9 per cent. This may also be corrected. One patient was delivered spontaneously, her cardiac condition undiagnosed at this

time. Two months later she was readmitted because of femoral thrombophlebitis. The complicating cardiac condition was now diagnosed for the first time, and she died later as a result of pulmonary embolism. A second patient, B. B., died in cardiac failure when eighteen weeks pregnant. The fetus was expelled just at the moment of death.

We do not intend to draw any conclusions from these figures in favor of or against any particular form of delivery. Each case presents an individual problem. However, we feel that it is of some interest to report that our most serious cardiac patients, i.e., the 5 patients grouped as Class 3, were delivered by the vaginal route. May it be stressed that they were considered too serious cardiac risks to be offered the "benefits" of cesarean section. One patient mentioned above, B. B., died in her fourth month; the other 4 survived. With the incidence of morbidity and the mortality rate significantly higher following cesarean section, and since cardiac failure is a rarity during labor, it has been our policy to favor, from a cardiac standpoint, vaginal delivery.

SUMMARY AND CONCLUSIONS

1. Three hundred forty-five cases of pregnancy complicated by rheumatic heart disease are reported.

2. Seventy-seven cardiac failures occurred in this group, an incidence of 22.3 per cent. We feel that it is possible to foretell fairly accurately which patient with heart disease will fail unless adequate bed rest is enforced. Several prognostic aids are offered.

- a. The functional capacity of the heart in the nonpregnant state is of great importance, 83 per cent of the failures occurring in the badly incapacitated groups, 2B and 3, while only 17 per cent of the failures were in the comparatively well-functioning Classes 1 and 2A.

- b. An equally important aid is the patient's age; 42.6 per cent of the pregnancies in women over thirty years of age were complicated by cardiac failure as compared to 16.1 per cent in the group under thirty.

- c. A third significant aid in prognosis is the presence or absence of a history of previous failure. Of those that decompensated before, 75 per cent had cardiac failure when pregnant as compared to a 14.1 per cent incidence of cardiac failure in the previously compensated group.

We feel, therefore; that the patient whose measure of functional capacity places her in the relatively severe grades of heart disease, the cardiac patient who is more than thirty years of age, the cardiac patient who gives a history of previous decompensation, should be willing, if she wishes to assume the burden of pregnancy, to submit to frequent antenatal observations from the very beginning of her pregnancy and she must be willing and able to spend the greater part of the pregnancy at absolute bed rest if necessary. The number of pregnancies borne by women with rheumatic heart disease, in itself, is apparently of no consequence. The multigravid, however, will more commonly fall into one or more of the three groups mentioned above.

3. The incidence of cardiac failure in pregnancy can be reduced markedly if the general principle of early and absolute bed rest is adhered to. We have had two failures in our last 103 cases, and one of these was possibly preventable.

4. Eighty per cent of the 77 cardiac failures that were seen at this hospital occurred before the last month of gestation. Acute failure during labor is a rarity. Our clinical experience follows very closely the physiologic changes which indicate that pregnancy exerts a steadily increasing circulatory burden, beginning when the pregnancy begins and reaching a maximum during the eighth month. A lightening of this circulatory load occurs during the period four to six weeks preceding delivery with a consequent clinical improvement. Therefore, we feel it unwise to resort to late pregnancy terminations and follow the general rule of allowing the gestation to go to term.

5. Each pregnancy presents an individual problem in the management of labor. In our series, 8.4 per cent of the patients were delivered by the abdominal route and 91.5 per cent were delivered vaginally. Since the incidence of morbidity, as expressed by fever with its concomitant elevation in pulse rate, and the mortality rate are significantly higher following cesarean section; and since cardiac decompensation is a rare accident during labor, we feel that the "burden of proof" lies with cesarean section. This consideration applies only to section for the cardiac condition "per se." Patients who have had the benefit of treatment, and go into labor well compensated, may in general be handled on the basis of obstetric indication, essentially as though not suffering from heart disease.

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These three patients had typhoid fever associated with vaginal or uterine bleeding. Incidentally, because of this bleeding two of these patients had been assigned to the gynecologic ward. In all three cases *B. typhosus* had been obtained in pure culture and the Widal had been positive although only later in the disease. All three patients had an irregularity of the menstrual cycle; one had metrorrhagia during the first and second weeks of the disease; one had menorrhagia and the third patient had an abortion five months previously, but the typhoid fever was ushered in by profuse bleeding. This latter patient died and autopsy revealed a typical nonpregnant uterus with no evidence of remnants of a pregnancy.

The authors believe that the excessive uterine bleeding in these patients was a part of the disease, and did not represent the rare hemorrhagic type of typhoid fever. The importance of the symptom of vaginal bleeding lies in the possibility of confusion in diagnosis. Therefore, menorrhagia and metrorrhagia should be borne in mind in the diagnosis of typhoid fever in women. Abnormal uterine bleeding in typhoid fever probably is encountered more frequently than the literature would indicate.

WILLIAM B. SERBIN.

THE EFFECT OF PREGNANCY ON EXPERIMENTAL HYPERTENSION*†

WITH OBSERVATIONS ON THE EFFECTS OF DECIDUOMAS

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WOMEN who begin pregnancy with arterial hypertension usually undergo a progressive rise of blood pressure as the pregnancy advances. This is true with essential hypertension, and is particularly true in cases of chronic Bright's disease. Severe hypertension of any origin is considered by Herrick¹ and many others to be a strong indication for therapeutic abortion. Exceptional cases occur of hypertensive women whose blood pressure declines during pregnancy.

In order to study the factors which might be responsible for this unfavorable influence of pregnancy upon human hypertension, it would seem important to examine the effects of pregnancy upon both the course and the onset of hypertension induced experimentally in animals.

Few observations on this subject have been reported. Dill and his collaborators² have stated that dogs and rabbits are more susceptible to renal ischemia during pregnancy, both species developing an "eclamptic-like syndrome characterized by hypertension, albuminuria, coma, convulsions and death," and that such a syndrome did not occur in their nonpregnant control animals. Goldblatt, Kahn and Hanzal,³ on the other hand, found that pregnancy produced a slight or moderate fall of blood pressure in hypertensive dogs, and they attribute this to the compensatory action of the fetal kidneys. Similar observations on dogs have been made by Dawson, Cressman and Blalock^{4a} and by I. H. Page.^{4b} In hypertensive rats a lowering of blood pressure during pregnancy was recorded by Harrison, Grollman and Williams,⁵ and they likewise attributed the effect to an antipressor action of the fetal kidneys. Indeed, Goldblatt⁶ states that pregnant dogs can withstand a degree of renal ischemia which nonpregnant females would be unable to tolerate.

There is, then, a lack of agreement as to the effect of pregnancy upon the course of experimental renal hypertension, and there is much uncertainty as to the interpretation of the various findings.

METHODS

Rats and rabbits were used because of their convenient breeding habits. The rabbits were kept in individual cages on a diet containing 12 per cent protein. Blood pressure was determined on the central artery of the ear by the method of Grant and Rothschild⁷ without anesthesia. Pregnancies were induced at the proper time by mating with bucks of known fertility, and pseudopregnancies were induced by

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mating with sterile bucks. In rabbits hypertension was produced by partial ligation of the renal arteries, following the details described in a previous communication.⁹

The rats, of the Long-Evans strain, were housed in groups of four and maintained on a diet containing requisite food factors including 18.5 per cent protein. Blood pressure was measured without anesthesia by the tail plethysmograph method described by Williams, Harrison and Grollman.⁸ In rats persistent hypertension was produced in two ways: (a) By partial ligation of one renal artery to 0.3 mm. according to the technique of Wilson and Byrom,¹⁰ using a silk ligature over a wire of known diameter; and (b) by our own modification of a method similar to that used on dogs by I. H. Page¹¹ and by Greenwood, Nassim and Taylor.¹² The technique consists of painting one kidney (explanted subcutaneously to avoid intestinal adhesions) with collodion and removing the opposite kidney one to four weeks later. Each method produced sustained hypertension in about two-thirds of all operated rats.

In some instances pregnancy was induced after the blood pressure had reached a hypertensive level; in other instances the renal surgery was performed at various stages of pregnancy in order to compare the results with those of Dill and Erickson.² It was noted that many hypertensive rats were refractory to mating because of a cessation of estrus cycles, the latter finding having been noted by Diaz and Levy.¹³ Since all of the hypertensive rats lost some weight, and since this estrus inhibition was particularly noticeable in those which lost a great deal, its mechanism is probably the same as that described for inanition,¹⁴ namely, a failure of the hypophyseal gonadotropic function. In some animals, therefore, 10 rat units of gonadin were injected to induce estrus. In a further group of 12 hypertensive rats, pseudopregnancies were induced by stimulation of the cervix with a glass rod or an electric current. Deciduomas were then produced by placing four or five silk threads through each uterine horn four to five days after induction of pseudopregnancy. The existence of the placentomas was checked later by exploratory laparotomy.

RESULTS

1. *Blood Pressures of Normal Rabbits and Rats, and the Criteria for Hypertension.*—The normal systolic pressure in the ears of the rabbits used varied from 70 to 103 mm. Hg (median value 76). Since the values are fairly constant for any one rabbit, a rise greater than 20 mm. Hg above the basal level maintained for two consecutive occasions on different days was accepted as hypertension.

The mean of the tail blood pressures on a random sample of 21 rats, using the last 3 of 7 biweekly readings on each rat was 104 mm. Hg with a standard deviation of 5. Rats giving three consecutive readings over 120 (three times the standard deviation above the mean) several days apart were considered hypertensive. The hypertension following unilateral renal artery constriction was sometimes marked (over 200 mm. Hg) and persisted indefinitely (six months or more). The rats thus differ from dogs and rabbits in which the presence of a normal kidney usually causes a disappearance of the hypertension. In three rats with marked hypertension and rapid wasting, the blood ureas were found to be only slightly elevated (62 mg. per cent); so marked azotemia is not necessarily present in this type of hypertension.

2. *Normal Animals During Pregnancy.*—There have been numerous studies of the effect of pregnancy on the blood pressure of normal women (summarized by Jensen¹⁵), and although there is no significant change in the systolic pressure, there is a slight lowering of the diastolic pressure. We have found no references regarding the effect of pregnancy on the blood pressure of any animals except for our own studies¹⁶ on rabbits in which we found the blood pressure unchanged. The influence of pregnancy on the blood pressure of normal rats is being investigated further.

3. *Renal Ischemia Induced During Pregnancy.*—In a group of 18 rats, the left renal artery was constricted to 0.3 mm. under identical conditions. Eight of these animals were in various stages of pregnancy at the time of surgery, six becoming hypertensive. The important finding was a delay in the onset of hypertension until

after parturition, compared with the usual rapid onset (see Figs. 1 and 2). This suggests that rats are less susceptible to renal ischemia when pregnant. In rabbits, our experience indicates that the effects of partial ligation of the renal arteries are no different in pregnant than in nonpregnant animals.

4. *Pregnancy in Hypertensive Rabbits.*—In 12 rabbits, pregnancy was induced after the production of hypertension by the methods outlined. Nine showed no consistent change during pregnancy and in three there was a slight fall.* Four

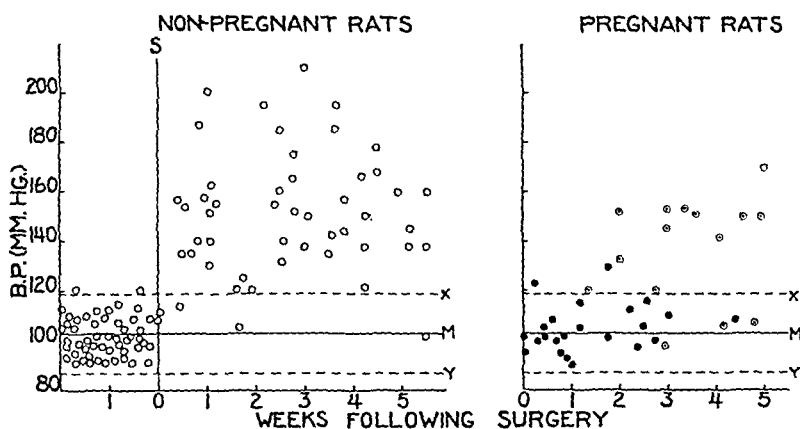


Fig. 1.—Delay in onset of hypertension following renal ischemia produced during pregnancy. ○, nonpregnant rats. ●, pregnant rats. ⊙, post-partum rats.

This notation continues through all the figures. Ordinate 0 represents surgery. The value M is the mean normal blood pressure for a group of 21 rats. Lines x and y are ± 3 standard deviations from this mean (see text). Note that nearly all the measurements in the first week following surgery are hypertensive in the nonpregnant group, whereas only 1 reading in the first week is hypertensive in the group of pregnant rats.

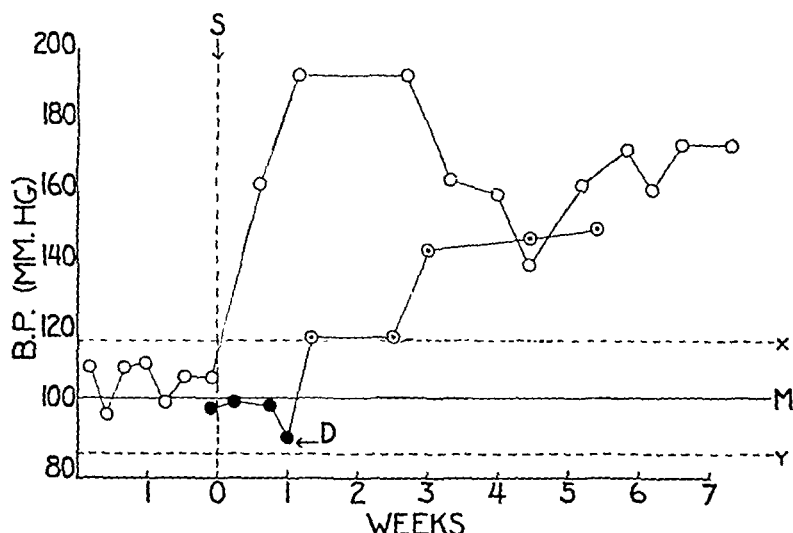


Fig. 2.—Comparison of immediate effect of renal ischemia on a pregnant and a non-pregnant rat. Symbols as in Fig. 1. D , represents day of delivery.

of these experiments are illustrated in Fig. 3. Neither the blood pressure changes, the appearance of the animals, nor their behavior differed in these hypertensive pregnant rabbits from those observed in the normal pregnant rabbits previously reported.¹⁶

5. *Comparison of Effects of Pregnancy and Dietary Load in Rabbits With Limited Renal Blood Supply.*—The above 12 rabbits were subsequently placed on a

*In an independent study, as yet unpublished, Dr. John D. Corbit at the University of Pennsylvania Medical School has essentially the same findings.

diet enriched with enough casein to double the original (12 per cent) protein content. Whereas pregnancy had not affected them adversely, the increase of dietary protein caused illness and death in a third of the animals. This indicates that increasing the load on the ischemic kidney produces detrimental effects which these same animals had not shown during their pregnancies.

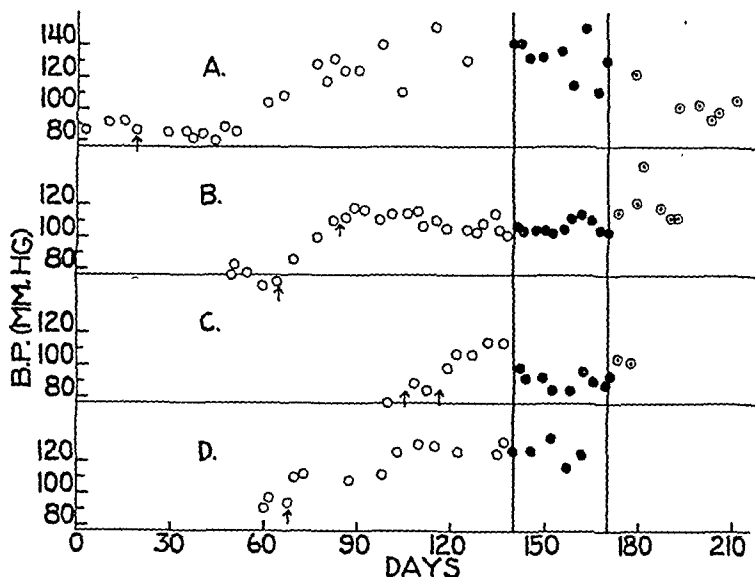


Fig. 3.—The influence of pregnancy on rabbits with experimental hypertension. Serial observations on 4 selected animals. Notations as in previous figures. Arrows indicate surgery. Vertical lines indicate beginning and end of pregnancy.

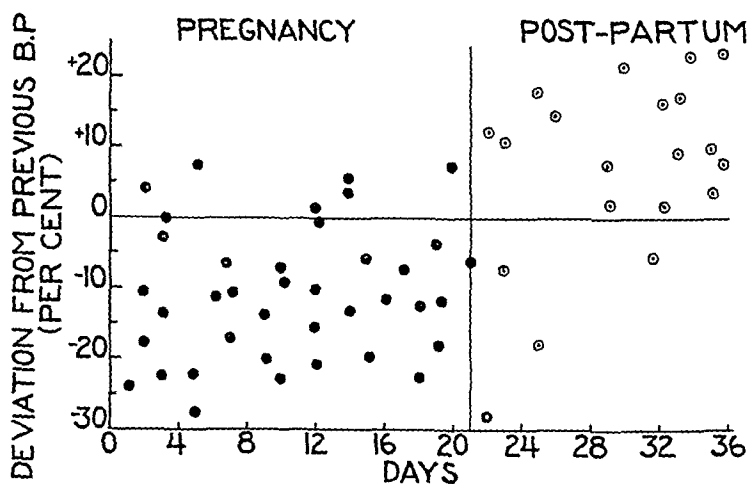


Fig. 4.—Influence of pregnancy on previously hypertensive rats. Notations as in previous figures. All values are expressed as a percentage deviation from the mean of the 3 readings immediately preceding mating for each animal. Note the return to a hypertensive level following delivery (vertical line at twenty-one days). Ordinate 0 represents day of mating.

6. *Pregnancy in Hypertensive Rats.*—Ten of the hypertensive rats were successfully mated and their blood pressures followed during pregnancy and the puerperium. In every case there was a definite fall of blood pressure during pregnancy with a return after delivery. This fall was often observed during the first third of pregnancy, even before implantation of the ovum occurs. In Fig. 4, illustrating this phenomenon in the whole group, it may be seen that almost all of the observations during pregnancy fall below the zero line, which represents the mean of three readings taken immediately before pregnancy in each rat.

7. *Pseudopregnancy With Deciduomas in Hypertensive Rats.*—The behavior of the blood pressure in a group of 11 rats, in which deciduomas were produced, showed a very striking resemblance to that of the pregnant animals, as may be seen by a comparison, of Figs. 4 and 5. Note that the decline in blood pressure occurred within a few days after induction of pseudopregnancy, often before the threads were placed through the uterus. When stimulation of the cervix did not induce pseudopregnancy, and the insertion of threads in the uterus did not produce deciduomas, as shown by subsequent laparotomy, such a decline of hypertension did not occur.

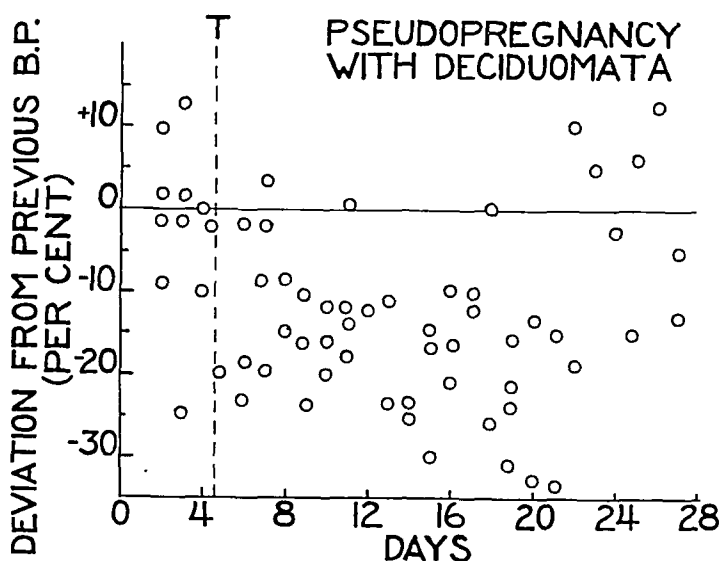


Fig. 5.—Influence of pseudopregnancy with deciduomas on previously hypertensive rats. Details of legend as in Fig. 4. Ordinate 0 represents artificial induction of pseudopregnancy. Note tendency to return toward the hypertensive level during the fourth week. On the fifth day following artificial induction of pseudopregnancy (ordinate T) threads were placed in the uterine mucosa to produce deciduomas.

DISCUSSION

It would seem that rats and rabbits are less susceptible to renal ischemia when pregnant inasmuch as it has been found more difficult to produce hypertension during pregnancy. The findings are in contrast to those reported by Dill and Erickson² but support the observations of Goldblatt.⁶ Pregnancy, furthermore, lowers the blood pressure in experimental renal hypertension, although the effects are more pronounced in rats than in rabbits. This is remarkably at variance with the often disastrous influence of pregnancy upon renal hypertension in women. If this is truly a species difference, it is very important to know what factors account for it.

There are several possible explanations for the lowering of blood pressure during pregnancy in hypertensive animals. First, there is the explanation advanced by Goldblatt³ and by Harrison, Grollman and Williams⁵ that the fetal kidneys cause a lowering of the hypertension through some compensatory action. This explanation, however, could not account for the decrease in the hypertension which we found to follow the onset of pseudopregnancy with deciduomas in rats; nor could it explain the decrease in hypertension which was found to precede the implantation of the ovum and to precede by far the development of a

functioning kidney. It is therefore necessary to search for another explanation.

Another point of view which has not hitherto been adequately considered concerns the relationship of the degree of hypertension to variations in the load on the kidneys during pregnancy. The feeding of high nitrogen diets to hypertensive animals has been said to cause a rise of blood pressure¹⁷ or an increased mortality (see pages 55 and 56) presumably because of the increased nitrogenous load on the kidneys. During pregnancy, however, due to the marked storage of protein with resulting diminution of nitrogen output, the load on the kidneys may actually be decreased. It has been shown by Walter and Addis,¹⁸ for example, that the ratio of kidney weight to body weight, which is one index of renal work, is considerably less in pregnant rats at term than in normal controls. Nitrogen balance studies on normal pregnant women have shown an actual decrease in the nitrogen output and there is, in addition, a lowered nonprotein nitrogen level in the blood. Inasmuch as the real osmotic work of the kidney is nearly proportional to the nitrogen excretion,¹⁹ it would seem that pregnancy alone would not constitute a "burden" upon the excretory function of the kidneys even in human beings.

This point may be unsettled, but the statements by Kellogg,²⁰ Dieckmann,²¹ Stander,²² and indeed in most textbooks on obstetrics, that the exacerbation of hypertension in nephritis is due to the "burden of pregnancy on the kidneys" might well undergo critical re-examination. The direction of change in osmotic work imposed upon the kidneys during pregnancy may, of course, vary with the amount of protein in the diet, but the magnitude of such alterations would be small and probably negligible. The contrast between human beings and the experimental animals here considered makes it unlikely that this is the principal factor involved. Certainly one must look for some other factor to explain the almost invariable increase of hypertension in pregnant women in view of the almost invariable reduction of hypertension in pregnant or deciduomatous rats.

The concept that a "low reserve kidney" might account for a rise of blood pressure during late pregnancy is still firmly entrenched in obstetric literature. Certainly the partial renal artery ties, subtotal nephrectomies and other procedures utilized for the production of hypertension constitute experimentally produced kidneys of "low reserve." Even though the hypertension of rabbits may have subsided, we have shown above that loading their kidneys with an increase in dietary protein may cause sickness and death; yet pregnancy alone even in the same animals will cause neither.

A third explanation for the lowering of experimental hypertension during pregnancy concerns the hemodynamic changes which follow the insertion of placentas into the circulatory apparatus. The placentas of rats, rabbits, and human beings, though differing somewhat in vascular arrangement,²³ may all constitute a low resistance shunt which decreases the peripheral resistance and probably accounts for the lowering of diastolic pressure during normal pregnancy. Such a concept has been

emphasized by Burwell.²⁴ This circulatory factor is by no means eliminated, since it is also probably active when the highly vascular deciduomas are induced in rats.

Common factors which do exist in all three conditions (i.e., pregnancy, pseudopregnancy, and deciduomas) are the endocrine changes which are at least qualitatively similar. It would seem likely therefore that such endocrine changes might be concerned with the lowering of blood pressure. Inasmuch as the human placenta secretes its own gonadotropic hormone²⁵ which is not known to be produced by the placentas of animals other than primates, this is one difference between pregnancy in rodents and women which should receive due consideration. Experiments are in progress to determine the effects of pseudopregnancy alone and of the various sex hormones upon the blood pressure of hypertensive animals. There is very likely some humoral relationship between the placenta and the kidney, a relationship which may be of some importance in the study of the hypertensive disorders of pregnancy.

CONCLUSIONS

1. Pregnancy appears to have a beneficial effect upon experimental renal hypertension in the rat or rabbit.

2. When operations designed to limit the blood flow to the kidney are performed *during* pregnancy, the onset of hypertension is commonly delayed until after parturition; whereas it usually appears within a very few days after surgery in nonpregnant controls.

3. Pregnancy does not constitute a "burden" on the kidneys. This is indicated by the fact that animals with minimal amounts of functioning kidney tissue (i.e., experimentally produced "low reserve kidneys") do not exhibit hypertension during pregnancy, but when not pregnant may die when the excretory work of the kidneys is increased by adding more protein to the diet. Some factor other than increased renal work or "load" must explain the difference between hypertensive animals and hypertensive women during pregnancy.

4. Pseudopregnancy with deciduomas likewise lowers the blood pressure of hypertensive rats.

5. The possibility is suggested that either the endocrine or the circulatory changes associated with pregnancy, pseudopregnancy, or the decidual tumors are responsible for this effect, rather than any compensatory action of fetal kidneys.

SUMMARY

To shed light on factors possibly concerned with the unfavorable influence of pregnancy upon human hypertension, rats and rabbits with experimental hypertension were studied during pregnancy or pseudopregnancy with deciduomas.

Blood pressures were measured in rats by the tail plethysmograph and in rabbits by the ear capsule method. Hypertension was induced by partial ligation of renal arteries, or in some rats by painting one kidney with collodion and removing the opposite kidney later. Deciduomas were induced by placing silk threads in the uterine mucosa during pseudopregnancy.

During pregnancy in normal rabbits, the changes in blood pressure as shown by these methods are negligible. Renal ischemia produced during pregnancy was followed by hypertension, but the onset was delayed until after delivery. Pregnancy produced an early fall in blood pressure in all of 10 hypertensive rats and a less constant fall in 12 hypertensive rabbits. No untoward effects were observed. An increase of protein content in the diet caused sickness or death in hypertensive non-pregnant rabbits. Pseudopregnancy with deciduomas in all of 11 hypertensive rats caused a decline in blood pressure corresponding roughly in time and extent with that caused by pregnancy.

These findings suggest that the cause for the blood pressure fall observed more likely results from endocrine changes than from any action of fetal kidneys. Doubt is thrown on the concept that a "load on the maternal kidneys" plays a significant part in the exacerbation of hypertension usually observed in human pregnancy.

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II. THE CLINICAL AND LABORATORY DIFFERENTIATION OF SPONTANEOUS AND INDUCED ABORTION*

A STUDY OF 502 CASES

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THE diagnosis of abortion is beset with several minor and one major difficulty. Ordinarily, the familiar history of a period of amenorrhea followed by abdominal cramps, vaginal bleeding, and the passage of clots with or without a recognizable fetus makes it clear that conception has occurred and that the normal course of gestation has been interrupted at an early stage. Ordinarily, it is also easy to determine whether the abortion is threatened, inevitable, incomplete, complete, or missed.

In a fair number of cases, however, one may be misled in arriving at even this simple diagnosis. Ectopic pregnancy may masquerade for a time as threatened or inevitable abortion. Hydatidiform mole may do the same. Menorrhagic and metrorrhagic conditions unassociated with pregnancy may lead to errors in diagnosis as may also the first hemorrhagic episode of a submucous fibroid or carcinoma of the corpus.

But to differentiate between spontaneous and induced abortion is the major difficulty. This is one of the rare instances in which the patient usually knows the diagnosis and the physician does not. If patients always told the truth there would be no problem. Everyone who has had experience with the aftercare of abortion is aware, however, that a patient who is perfectly frank and trustworthy about all other matters may lie blandly and persistently on this point alone. And it is a point of great significance for the management of the case and for its prognosis. Many authorities go so far as to say that the patient's statement per se is worthless unless she admits induction. The inference that induced abortion is far more frequent than hospital records indicate is almost universal.

A remarkable exception is found in Pearce,¹ who states that in the neighborhood of St. Giles Hospital, London, where his study was made, emmenagogue pills are taken as routinely for delayed menstruation as laxatives for constipation. He goes on to state his belief that "induced abortion is certainly much less frequent than these figures taken at their face value would suggest. Idiopathic abortion is so common and the human characteristic of rationalization so strong that any estimation of the proportion of criminal abortion is well nigh impossible. Many of the noxious things were taken and done in innocence, sometimes the woman not knowing she was pregnant." This is the view that would consider any abortion spontaneous until proved to be induced. It is rare. The reverse is

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usually held. Most recent writers have wisely abandoned the old, simple and patently fallacious method of considering fever proof-positive of illegal interference. Bouleware,² Pasmore,³ Simons,⁴ and others have pointed out the presence of septic signs in incomplete spontaneous abortion with sapremia. Cook⁵ observed a typical septic course in a patient who aborted spontaneously while on the medical ward under treatment for cardiac disease. Studdiford⁶ in an earlier study reported two similar cases.

By whatever path one approaches the task of classification on this point it becomes evident that no clear-cut grouping can be made. The group who frankly admit mechanical induction may be taken as the "purest" from which one should be able to derive criteria for determining objectively the truth or falsehood of a claim to spontaneous abortion. Unfortunately no such clear-cut criteria can be so derived. While statistically this group does show a higher frequency of fever, low sedimentation rate, acute inflammatory reaction in decidua and chorion, etc. (Tables I and II), there are individual cases which exhibit none of these. On the other hand, all of these evidences of infection are to be found among those who most convincingly deny any kind of intentional interference. A clean curettage by a skilled abortionist is obviously no more liable to infection than a therapeutic abortion performed in our own operating room. Conversely, an incomplete spon-

TABLE I. PATIENT'S STATEMENT OF TYPE OF ABORTION, EXAMINER'S ESTIMATE OF VERACITY, PATIENTS WITH TEMPERATURE 100.4° F. OR ABOVE, PATIENTS WITH SEDIMENTATION RATE LESS THAN 40, PATIENTS TREATED BY CURETTAGE

TYPE OF ABORTION	CASES	%	FEBRILE	%	LOW SR	%*	CURETTED	%
Induced (mechanical)	52	100	18	35	19	44	30	59
Spontaneous (false)	32	100	8	33	14	50	18	59
Spontaneous (doubtful)	156	100	32	22	43	35	101	64
Induced (drug)	104	100	20	18	32	35	71	68
Spontaneous (true)	158	100	24	14	25	20	113	71
Totals	502	100	102	20	133	26	333	67

*Per cent of cases in which sedimentation rate was reported.

TABLE II. STATED INDUCTION BY PATHOLOGY REPORT

PATHOLOGIC DIAGNOSIS			DIAGNOSIS FROM HISTORY					
	CASES	%	INDUCED (MECH.)	%	INDUCED (DRUG)	%	ALL SPONTA- NEOUS	%
No report (not curetted)	170	34	21	41	34	32	115	33
Acute inflammation of decidua and chorion	53	10	10	18	9	9	34	10
Degeneration of decidua and chorion	204	41	15	29	48	46	141	41
Normal pregnancy	9	2	1	2	3	3	5	1
Normal endometrium	25	5	1	2	3	3	21	6
Endometritis	15	3	1	2	2	2	12	4
Cystic and glandular hyperplasia	4	1	--	--	1	1	3	1
Placental polyp	13	2	--	--	3	3	10	3
Endometrial polyp, endocervicitis, etc.	6	1	1	2	1	1	4	1
Autopsy, only*	3	1	2	4	--	--	1†	--
Totals	502	100	52	100	104	100	346	100

*In 2 cases death was preceded by curettage. Total autopsies 5.

†Not pregnant.

taneous abortion offers the same nidus as retained secundines post partum. The uterus recognizes no moral distinctions.

Even microscopic study of curettings does not answer the question, "Induced or spontaneous?" although it sometimes corrects the clinical diagnosis of "abortion." Four cases, typical of many, serve to illustrate this point.

CASE 1.—(Fig. 1.) M. B., married, aged 22, para i, gravida ii, bled for three weeks at the fourth month of her previous pregnancy and was treated for threatened abortion by hospitalization at New York Women's Infirmary. She carried to term and was delivered of a normal child. Last menstrual period occurred on March 10, 1938. This was a planned pregnancy. She was cleaning house on May 28,



Fig. 1.



Fig. 2.

Fig. 1.—Degeneration and acute inflammation of the decidua.

Fig. 2.—Marked degeneration of decidua and early placenta.

and became dizzy and began to bleed at 7 P.M. At 9 P.M. severe cramps began and the next day clots were passed. Curettage on May 31 revealed degeneration and acute inflammation of the decidua. This patient gave a most convincing history of spontaneous abortion. Her course while in the hospital was afebrile; white blood count 10,100, polymorphonuclear leucocytes 62 per cent; sedimentation rate one hour; Wassermann negative; hemoglobin 80 per cent.

CASE 2.—(Fig. 2.) J. D., married, aged 30 years, para ii, gravida iii, had her last menstrual period on Dec. 28, 1938. She had used no contraceptive. She did a heavy washing, took a hot bath, and a dose of castor oil to induce abortion on March 6, 1939. This was followed immediately by the onset of cramps and spotting. On March 9 bleeding became profuse and clots were passed. Curettage on March 10 revealed marked degeneration of decidua and early placenta.

CASE 3.—(Fig. 3.) I. P., married, aged 23 years, para 0, gravida 0, had her last menstrual period on Oct. 3, 1938. Menstrual periods previously had been regular. She suffered a fall on December 3 and immediately had cramps and spotting fol-

lowed on the same day by profuse bleeding and the passage of clots. Curettage on December 4 revealed a normal early proliferative endometrium.

CASE 4.—(Fig. 4.) M. B., married, aged 33 years, para i gravida ii, had her last menstrual period on April 15, 1938. She had planned for this pregnancy. On June 20, for no apparent reason, she began spotting and having cramps. Three hours later bleeding became profuse and the next day several large clots were passed. Curettage on June 24 revealed cystic and glandular hyperplasia of the endometrium.

We can proceed then to a statistical analysis of admittedly impure groups, recognizing the probability that an indeterminate number included in the spontaneous group have actually undergone some form of mechanical interference, but with the growing conviction that the proportion of these is probably smaller than some authors have supposed.



Fig. 3.

Fig. 3.—Normal early proliferative endometrium.



Fig. 4.

Fig. 4.—Cystic and glandular hyperplasia of endometrium.

The cases upon which this study is based were 502 patients admitted to Bellevue Hospital because of illness associated with the early interruption of pregnancy. I have already reported the sociologic and psychologic characteristics of this group. The 35 cases of therapeutic abortion included in the previous series have been excluded from the present one, which consists of 346 (69 per cent) who claimed to have had spontaneous abortions, 104 (20.7 per cent) who admitted having used medical means to interrupt an unwanted pregnancy, and 52 (10.3 per cent) who confessed to mechanical interference.

Those who admit induction by means of drugs present an interesting situation. In the first place the group probably includes a number whose induction was actually mechanical. This is because drug induction does not seem to carry with it the same moral odium as does me-

chanical interference, and also because its admission does not implicate the abortionist whom the woman, whether from fear or gratitude, feels compelled to shield. Second and far more important, this group, on statistical analysis, shows highly significant correlations with that which we have classified as "spontaneous-true," i.e., that in which any kind of induction was most convincingly denied. Two groups classified according to the investigator's impression of the patients' reliability as "spontaneous-false" and "spontaneous-doubtful" assume intermediate positions. Reference to Table I will make clear the gradations from "induced-mechanical" to "spontaneous-true" and will show that according to these criteria "induced-drug" belongs almost at the opposite pole from "induced-mechanical." Whatever the patients' motives and intentions, she has in all probability undergone a spontaneous abortion coincidental with, but only slightly, if at all, influenced by the efforts she has made to avert the birth of an unwelcome child. In the "induced-drug" group are included not only those who took various medications by mouth but also those who soaked in hot baths and plied themselves with douches and enemas. (Douches in which the patient thought the nozzle had entered the cervical os and reported an immediate uterine cramp were considered mechanical interference.)

This finding furnishes strong confirmation of the opinion that efforts which fall short of invasion of the uterus are powerless to expel normal products of conception from a woman who is not predisposed to abort. Patients in whom such invasion is neither admitted nor strongly suspected correspond statistically in all ways, except the purely psychologic, to the spontaneous group. This is a point of major importance for treatment and prognosis.

The patient's statement as to whether her abortion was spontaneous or induced is not the only point in the history which can give a clue to the actual condition. Obviously a history of debilitating disease or of trauma should be given some weight, though these are perhaps fully as likely to figure in the fiction of one who would conceal induction as in the straightforward story of one who has lost her fetus involuntarily.

Of the 346 patients who claimed that abortion was spontaneous, 105 (30 per cent) could assign no cause for the onset of symptoms; 123 (36 per cent) spoke of over-exertion: climbing stairs, heavy lifting, laundry work, and the like; 47 (14 per cent) could point to some trauma such as a fall or a blow on the abdomen; violent emotions, especially fear or anger, were mentioned by 19 (5 per cent); and 52 (15 per cent) named a variety of other precipitating factors: coitus, heat, cold, malnutrition, "weakness," etc. It is curious that these various "causes" were distributed with equal frequency throughout the months of early pregnancy. It seems likely that, at least statistically, they may have been rationalizations in the same sense as in the drug inductions. There can be little doubt that abortion may be precipitated by any one of them, but whether this can occur with a healthy fetus in a woman not predisposed to abort is another question.

The history of previous spontaneous abortions offers evidence in support of the contention that the current one is also spontaneous. One-

third of the patients who claimed to have had a spontaneous abortion at this time and who had previously been pregnant gave a history of one or more previous spontaneous abortions. Only 10 per cent of previously gravid patients who admitted mechanical interference in the current pregnancy presented such a history. Twenty-nine per cent of the latter, however, admitted previous mechanically induced abortion while but 5 per cent of the former did so. This fact is opposed to the belief sometimes voiced that induced abortion is likely to be followed by "miscarriage" in subsequent pregnancies.

It is often said that first pregnancies are more likely to terminate in spontaneous abortion than are subsequent gestations. This statement is not confirmed by the present data. In our series there were 114 primigravidas. Thirty-two per cent admitted induction and 68 per cent denied it. Of the 388 patients who had previously been pregnant, 74 (19 per cent) gave a history of abortion in their first pregnancy. Fifty-three (71 per cent) said that this termination was accidental, or in other words, 13 per cent of first pregnancies in the previously gravid group ended in spontaneous abortion. These 388 women had had an aggregate of 1,240 pregnancies prior to the current gestation. Of the 852 pregnancies which were of higher order than the first, 245 (27 per cent) ended in abortion. One hundred thirty-six (55 per cent) were said to be spontaneous, 109 (45 per cent) induced abortions. If the pregnancies voluntarily interrupted are excluded from the calculation, we find that 17 per cent of all pregnancies of higher order than the first ended in spontaneous abortion. It must be supposed, for reasons already stated, that a certain number of the past abortions reported as induced were in reality spontaneous. The reverse is not nearly so likely in the past history as in that relating to the current illness.

Turning from the history to the clinical course, we find that 35 per cent of the group admitting mechanical induction had temperatures of 100.4° F. or over, while the spontaneous and drug-induced groups each had but 18 per cent febrile cases. The former group had proportionally four times as many patients with temperatures above 103° F. as the two latter groups. Only 14 patients in the entire series, however, exhibited this grade of pyrexia.

Hemorrhage played a minor role in the morbidity of these patients. In spite of the ready availability of bank blood for transfusion, this procedure was thought advisable in only 14 cases. Only 19 patients exhibited hemoglobins of 50 per cent or lower (Sahli). These did not belong predominantly to any one of the three categories. When hemoglobins of 70 per cent and over were considered, however, it was found that 82 per cent of the spontaneous group, 79 per cent of the drug-induced, and 72 per cent of the mechanically induced group showed this finding.

The white blood count showed significant differences according to the history given by the patient. Fifty per cent of counts on patients admitting mechanical induction showed a leucocytosis of 12,000 or more, with 80 per cent or more polymorphonuclears. Twenty-seven per cent of counts on the spontaneous group and only 17 per cent of those on the drug-induced group presented this finding.

It is now generally recognized that syphilis does not play the prominent role that was once attributed to it in the etiology of spontaneous abortion. In this series, 4 per cent of routine Wassermann tests were found to be strongly positive and 1 per cent doubtful. Drane⁸ and DePuy⁹ report similar frequencies. Only 1 per cent of the mechanically induced group had positive Wassermans, while 5 per cent of each of the other two groups gave this evidence of syphilitic infection.

Much importance has been attributed to the cervical culture as indicative of interference or non-interference. *Staphylococcus aureus* has been considered proof positive of unskilled manipulation, and *Streptococcus hemolyticus* indicative of unclean instrumentation. No strong evidence for these views could be found in the present study. The former organism was found in 46 cultures distributed proportionately through all groups classified according to history of type of abortion. Only two of the 46 had temperatures of 103° F. or above. Both admitted mechanical induction. One of these died of subacute bacterial endocarditis, the blood culture being positive for *Streptococcus viridans*. Streptococci appeared in only 6 cervical cultures. Of the 3 cases in which viridans were found, 2 denied induction. One of these had an afebrile course, the other a moderate febrile reaction (100.4° to 102.8° F.). The third, who admitted drug induction, had a temperature of 103° F. None was fatal. The three cultures which were positive for hemolytic streptococci all occurred in the group who gave a history of drug induction. Two were afebrile; one had a temperature below 102.8° F. All made uneventful recoveries. The other positive cultures reported were: 11 colon bacilli, 10 diphtheroids, and 1 gonococcus. These were not associated significantly with either of the induced nor with the spontaneous group. None of the patients harboring these organisms were seriously ill. Studdiford has pointed out earlier that many of the strains of bacteria present in the vagina are avirulent.⁶ We had no facilities for the routine culture of anaerobes. These were found in 92 per cent of cases showing positive cultures in Brown and Hunt's series.¹⁰

The fact that cervical culture gave little positive help in prognosis in this series should not lead to the conclusion that it is of no value. The negative finding is of considerable significance. Although no case of virulent hemolytic streptococcus infection happened to appear among the 502 cases reported here, since the completion of this study two have been seen who were so infected. It is felt that these patients owe their lives to the prompt recognition of the nature of the infecting organism (within twenty-four hours after admission) and the consequent prompt institution of appropriate therapy (sulfanilamide followed by curettage).

The management of these cases and the criteria for selecting those suitable for curettage have been described by Studdiford.⁶ The proportion of the mechanically induced group curetted (59 per cent) was substantially below that of the drug-induced (68 per cent) and the spontaneous (71 per cent).

The 13 febrile patients who admitted mechanical induction and who were curetted spent an average of 13.4 days in the hospital, while the

15 febrile drug-induced and subsequently curetted patients required but 8.5 days' hospitalization per patient, and the corresponding group who claimed spontaneous abortion remained only 6.7 days in the ward.

In every group except the mechanically induced, curetted afebrile patients were in condition to leave the ward earlier than those treated conservatively. This difference could be observed most strikingly in the drug-induced group (5.6 and 8.5 days, respectively). The reason for the exception in the mechanically induced group was that the 18 patients treated palliatively had, for the most part, such mild symptomatology that they were discharged the day following admission. Two refused examination and left the hospital immediately against advice and two were moribund on admission and died in a few hours.

The gross mortality for the entire series was 0.9 per cent (5 deaths). The operative mortality was 0.6 per cent. Four of the patients who died admitted mechanical induction. Two of these confessions were terminal after repeated denial. One patient steadfastly denied both pregnancy and induction and, indeed, no evidence of pregnancy was found at autopsy. No satisfactory explanation of her illness and death was arrived at, but since autopsy revealed peritonitis and acute nephritis and lead was demonstrated in her liver, the suspicion arose that death might have been caused by mistaken efforts to interrupt a non-existent pregnancy. If the latter controversial case is omitted, there was no mortality in 450 drug-induced and spontaneous abortions, while that in 52 mechanically induced, was 8 per cent.

SUMMARY

1. To differentiate abortion from other pelvic conditions is not always easy. Thirteen per cent of this series were erroneously diagnosed on admission. Without curettage, probably half of these errors in diagnosis would have remained unrectified.

2. To differentiate induced from spontaneous abortion is often impossible. No effort should be spared, however, in the attempt to learn the circumstances surrounding the interruption of pregnancy, since these have the greatest significance for prognosis. In this series the mortality in 10 cases admitting induction by a midwife was 30 per cent; in 13 cases induced by a physician it was 7.7 per cent; in 478 cases claiming self-induction or spontaneous abortion it was nil.

3. "Drug-induced" seems to be practically synonymous with spontaneous abortion, by every criterion except the purely psychologic. The two groups correspond closely in laboratory findings, clinical course, and outcome.

4. Thirty-three per cent of previously gravid patients who claimed to have had spontaneous abortions at this time gave a history of previous spontaneous abortion. Only 5 per cent of the comparable group who admitted mechanical induction gave such a history.

5. Induced abortion has been said to favor spontaneous abortion in subsequent pregnancies. In this series only 5 per cent of patients who claimed that the present abortion was spontaneous gave a history of past induction.

6. Spontaneous abortion was no more frequent in first pregnancies than in those of higher order. Induced abortion increased with order of pregnancy. That is, the probability of an abortion being induced, all things being equal, increases with the number of pregnancies the woman has previously undergone. This does not apply to pregnancies of very high order (10 or more). Of these there were too few in the present series to furnish a basis for conclusion.

7. Low sedimentation rate, fever, leucocytosis and acute inflammation of the decidua and chorion were found to be more frequently associated with mechanically induced abortion than with drug-induced or spontaneous. These evidences of infection were, however, by no means confined to the former group.

8. The Wassermann test was positive in 5 per cent of drug-induced and of spontaneous, in only 1 per cent of mechanically induced abortions.

9. Low hemoglobin determinations were not significantly more frequent in any one category than in the others.

10. Bacteriology showed little correlation with history in this series. The fact that here cervical culture cast scant light on differential diagnosis or prognosis should not lead to the conclusion that it is of no value. Infection with the virulent hemolytic streptococcus is relatively rare (it did not appear in this series), but its prompt recognition is of vital importance.

11. Curettage was performed in 59 per cent of the mechanically induced group, 68 per cent of the drug-induced, and 71 per cent of those claiming spontaneous abortion. Operative mortality was 0.6 per cent. Average stay in the hospital of curetted patients was five to seven days.

The author wishes to express her deep appreciation to Dr. William E. Studdiford for the photomicrographs illustrating this paper and for his interest and encouragement without which this study would not have been possible.

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Leo Loeb as the first showed that the uterus, if traumatized while under the influence of an active corpus luteum, responds by the formation of structure not unlike the maternal portion of the placenta. This growth may become quite large and assume the appearance of a decidual tumor.

Investigations by the writers demonstrated that uteri of postpubertal ovariectomized rats treated with daily doses of 100 gamma of estradiol, 3 mg. of testosterone, or 3 mg. of pregninolon are sensitized to local trauma in such a manner that gelatinous tumors of the endometrial mole type develop at the site of injury. These observations give further support to the concept that both local injury and an appropriately prepared humoral medium are essential for tumor production.

HUGO EHRENFEST,

PRIMARY SIGNET-RING CELL CARCINOMA OF THE OVARY

WITH A CASE REPORT

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WHEN Krukenberg in 1896 published his paper on five ovarian tumors which Marchand had offered to him for investigation and publication, he gave an accurate description both of the macroscopic and microscopic appearance of the new tumor but presented a deficient histogenetic explanation and a tentative and inaccurate definition. He suggested the term *fibrosarcoma ovarii mucocellulare carcinomatodes*. The consequence was that some of the various investigators who found and studied similar tumors after Krukenberg tended to do one of two things: Either they included cases which more or less differed from Krukenberg's material and therefore called them atypical Krukenberg tumors, or they enlarged the field of Krukenberg's entity. Unfortunately, different authors pursued different courses. The result is that at the present time, almost forty-five years after Krukenberg's original paper, we still lack a general and universally accepted conception of this tumor among gynecologists and pathologists.

Referring to Krukenberg's first suggestion of *fibrosarcoma ovarii mucocellulare carcinomatodes*, the outcome of all investigations carried out since Krukenberg's has proved that there is neither a fibroma nor a sarcoma present, that the mucinous cells are not specific, and that the carcinoma is a secondary one. To avoid committing themselves, many authors used the term "Krukenberg's tumor" without accurately explaining what they meant by this term. Prominent experts such as Frankl have expressed their dislike for the term "Krukenberg tumor" which is in agreement with the modern trend in nomenclature to avoid eponyms. The name Frankl suggested, which appears to be the most appropriate and accurate, is simply "metastatic carcinoma of the ovary" or eventually, "Krukenberg's metastatic carcinoma of the ovary." This latter expression implies a certain contradiction since Krukenberg himself doubted the carcinomatous character of the tumor and knew nothing of its metastatic origin. Schlagenhauser was the first to show that most Krukenberg tumors originated from an intestinal primary tumor growth; however, he still believed that the more rare true Krukenberg was primary in the ovary, but that it was frequently duplicated by a more common similar tumor which was a metastasis.

Not until done by Wagner, Cohn, Rosinski, and others was it definitely established that the overwhelming majority of these tumors are typically bilateral ovarian metastases of primary carcinomas of an intestinal

mucous membrane, most frequently of the stomach. This genetic definition is now generally accepted. The tumor usually produces a smooth, firm, uniform eccentric enlargement of both ovaries. It has a variegated cut surface due to frequent areas of microcystic changes and areas of intracellular mucinous secretion amid more solid areas of a fibrous type of tissue. Histologically the tumor is characterized by small cysts of mucin-producing epithelium and solid small clusters of similar columnar epithelial cells which as single cells invade the ovarian stroma diffusely and in large numbers. The stroma shows a reactive proliferation which misled Krukenberg and other investigators to describe a fibromatous or sarcomatous component.

Krukenberg described the signet-ring cells as specific for his tumor but already Marchand pointed out that such cells can be found not too rarely in the floor of mucin-producing adenocarcinomas, wherever they originate. One of us (W. S.) explained the transformation of mucin-producing columnar cells into signet-ring cells as a result of retained potency for secretion combined with a loss of polarity due to the embedding of the isolated tumor cells in the apolar stroma. We now know with certainty that signet-ring cells can be found with all mucin-producing carcinomas and even with chronic inflammation of mucin-producing mucous membranes, such as the uterine cervix or the pelvis of the kidney. We admit that signet-ring cells are characteristic but not specific for so-called Krukenberg tumors.

The above definition describes Krukenberg's tumor as an ovarian metastasis for which, in the overwhelming majority of cases, a primary tumor can be proved in the intestinal tract, either by clinical investigation or autopsy. Still, supporting Krukenberg's original conception, a few cases have been published which because of their histologic structure were classified as Krukenberg tumors without demonstration of a primary tumor. Such cases were called "*primary Krukenberg tumors.*" In this group only those cases can be correctly accepted in which the absence of a primary tumor was proved by autopsy or by the clinical observation that the patient was found well several years after simple extirpation of the ovarian tumor, which would have been impossible with an intestinal primary.

Cases of so-called primary Krukenberg tumors have been published by Glockner, Schenk, Marchand, Miner, Kruger, Frankl, and recently by Greenhill and Andrews.

Ewing, who himself has seen five cases of Krukenberg tumor and one primary carcinoma of the ovary with myxomatous changes, believes that true Krukenberg tumors are always secondary. He further believes that "primary carcinomas presenting this structure regularly yield areas of a different type." Masson interprets this concept as although "small portions of certain alveolar carcinomas of the ovary present the typical picture of Krukenberg tumors, there is little, if any, suggestion of glandular arrangement of cells in a true Krukenberg tumor." Masson's statement would reduce the field of true Krukenberg tumors considerably, for there are many cases which

present the combination of adenomatous structures with infiltrating signet-ring cells in varying proportions.

The common feature of all the case histories of "primary Krukenberg tumors" is the similarity of the histologic picture with the definitely established secondary carcinomas. On the other hand, and this should be emphasized, these tumors are definitely different from ovarian carcinomas which develop by malignant degeneration of pseudomucinous cystomas. The characteristic feature of the latter group is the presence of large cystic cavities separated by paper-thin septa, lined with a high columnar mucin-producing epithelium, and filled with thick mucinous contents. It is characteristic of these tumors that the stroma is in the background, and constitutes only a small part of the parenchyma; whereas, the overwhelming part of the tissue is represented by the epithelial cells and their product—mucin. It is characteristic of the secondary, as well as the primary, Krukenberg tumor that the stroma forms a great portion of the tumor. In fact the proliferation of stroma goes so far as to make the erroneous diagnosis of fibroma or sarcoma possible. The epithelial-lined cavities of Krukenberg tumors remain very small and their diameter barely reaches gross visibility. In spite of the most dense infiltration by signet-ring cells, the greater part of the tissue is still formed by the stroma.

The problem of the so-called primary Krukenberg tumor can be formulated as a question whether or not there is a possibility for the ovary to produce such a tumor from itself or by itself. As long as two or three observations were published, doubts as to whether these isolated observations are not due to incomplete search for a primary tumor seemed to be justified.

Since the number of well-established observations have increased to nine authentic and two doubtful cases, it seems justified to accept the statement that the ovary by itself can produce tumors (a) which morphologically duplicate the secondary metastases (b) of primary intestinal carcinomas. This manner of expressing these observations appears to be clearer than to speak of the existence of two types of Krukenberg tumors: The rare primary Krukenberg tumor (a above), and the more common secondary Krukenberg tumor (b above). We have had the opportunity of investigating one case which may be added to Group a.

CASE REPORT

A 61-year-old, obese, white female was admitted to the medical service of the Cook County Hospital, complaining of severe generalized abdominal pain. Thirty years ago she experienced her first acute attack of right upper quadrant pain. Ten months prior to admission she noted an increase in the intensity of the pain and a tendency for it to become generalized. For the past four months the pain was described as being continuous from morning until night, most severe over both right upper and lower quadrants. For the two weeks preceding admission she ate only soup, milk, water, and occasionally an egg, because of an anorexia. She further noted a progressively enlarging abdomen in recent weeks.

Physical examination revealed an extremely obese white female with a tensely distended abdomen, dyspnea, wheezing, and she complained of generalized abdominal

pain. Pulse was 88; respirations, 39 per minute; temperature, 99.2° F.; blood pressure, 136/90. The heart and lungs were normal except for the rapid respiratory rate and limited respiratory excursion. A ballotable mass was palpated in both upper quadrants which extended below the umbilicus on the right side. There was no tenderness or rigidity and bowel sounds were audible. A fluid wave could not be elicited. Pelvic examination was essentially negative. The extremities showed no edema and the reflexes were physiologic.

Examination of the blood revealed a hemoglobin of 58 per cent (Sahli), 3,720,000 red blood cells, and 13,950 white blood cells per cubic millimeter. A blood smear contained 84 per cent polymorphonuclear leucocytes, 10 per cent lymphocytes, and 6 per cent monocytes. The icterus index was 7. Nonprotein nitrogen was 39 mg. per cent and the creatinine was 1.6 mg. per cent. Blood diastase was reported as 16 units. The Wassermann test was negative. The urine was negative for albumin



Fig. 1.—Transverse colon with omentum, the latter thickened by the infiltrating tumor tissue. To show the thickness of the omentum a slice is cut out and placed beneath.

and sugar. The Graham-Cole test failed to visualize the gall bladder, and a flat plate of the abdomen revealed a marked hypertrophic arthritis of the spine and a peripheral displacement of the colon. An electrocardiogram showed a left axis deviation and myocardial damage as suggested by a flattening of the T-waves in all leads.

On the fourth day following admission a paracentesis was performed and approximately 5,000 c.c. of a hemorrhagic ascitic fluid was withdrawn from the abdomen. Three days later the patient developed symptoms of intestinal obstruction and vomiting which was overcome with nasal catheter suction siphonage and parenteral fluids. The patient grew progressively weaker and died on the fifteenth day of her stay in the hospital.

Autopsy Findings.—(Dr. J. D. Kirshbaum.) A layer of abdominal subcutaneous fat 68 mm. in thickness was present. The abdominal cavity contained over 3,000 c.c. of a hemorrhagic ascitic fluid. The omentum was transformed into a firm plaque of

tumor tissue filling both upper quadrants and extending down as far as about the level of the umbilicus. This plaque averaged 3 cm. in thickness and evidently was the ballotable mass palpated on abdominal examination. The mesentery of the transverse colon was transformed into another plaque of tumor tissue of similar thickness (Fig. 1). Numerous small tumor nodules studded the serosal surfaces of the small intestines and the pleural and peritoneal surfaces of the diaphragm. The peritoneum of the anterior abdominal wall and of the pelvis appeared to be free. The heart presented parenchymatous degeneration of the myocardium, and the lungs showed edema and passive congestion of all the pulmonary lobes. The pleura on the diaphragmatic surface of the right lower pulmonary lobe contained numerous small tumor deposits.

The gall bladder showed a marked hydrops. It measured 12 by 7.5 by 5 cm., and contained about 250 c.c. of a dirty grayish green inspissated material. The wall of the gall bladder was thickened up to 3 mm. and composed of grayish white material of firm consistency. Numerous pinhead to 3 mm. in diameter dark concretions were floating free in the gall bladder contents, but a 22 by 18 by 13 mm. concretion was impacted in the neck of the gall bladder. The mucosa of the gall bladder was smooth and glistening. The cystic duct showed an atresia at its



Fig. 2.—Uterus, tubes, and ovaries. The right ovary presents the primary carcinoma.

opening into the ampulla of the gall bladder which on careful microscopic examination showed chronic inflammatory changes without any evidences of tumor cells. The common bile duct was elongated and dilated but its lumen was free as were all the other extrahepatic bile ducts. By gross examination there was no evidence of carcinoma in the biliary tract.

The kidneys and the liver showed evidences of passive congestion. The spleen contained an ancient infarct.

The right ovary measured 5 by 4 by 3.5 cm. and contained several thin-walled cysts which projected above the surface. On cross section the ovary consisted of firm trabeculated yellowish-white tissue interspersed throughout by cystic cavities, from 2 to 20 mm. in diameter, filled with a mucoid material. The left ovary measured 4 by 1.3 by 1 cm. and on cross section was yellowish white and fibrotic; on gross inspection, it was apparently uninvolved by tumor tissue. The uterus was of normal size but beneath the perimetrium of the anterior fundic wall several up to 1 mm. tumor nodes were found (Fig. 2). The peritoneum of the vesicovaginal and rectovaginal septa contained plaques of tumor tissue.

The mucosa of the stomach was dark reddish brown in color, the folds and rugae were flattened, and the mucosa was smooth throughout. Its serosal surface was

studded by pinhead size tumor nodules. A single 5 mm. nodular peritoneal deposit protruded above the mucosal surface of the jejunum without ulcerating through it. The mucosal surface of the esophagus and duodenum was everywhere smooth. The mucosa of the ileum was smooth as was the mucosa of the large intestine. The pancreas and its ducts presented no changes.

An accurate detailed examination of the stomach, small and large intestines, gall bladder and bile ducts, and the pancreas and its ducts gave no evidence of a malignancy.

Microscopic Findings.—The right ovary (site of the tumor) was composed of a loose and partially edematous stroma which contained numerous irregularly shaped small cavities which were lined by low columnar epithelium, containing a pale staining granular cytoplasm. With the mucicarmine stain the cytoplasm of the epithelial cells presented red-staining mucin droplets, proving the mucinous char-



Fig. 3.

Fig. 3.—Right ovary; cystic and papillomatous tumor tissue, groups of typical signet-ring cells.



Fig. 4.

Fig. 4.—Right ovary, primary tumor presenting a labyrinth of small cystic cavities, lined with cuboidal or low columnar epithelium which forms low papillary projections.

acter of the cell. In many areas the epithelium of the cyst wall became many cell layers in thickness, the nuclei showed irregularities in size and shape, and the epithelial cells invaded and infiltrated the surrounding stroma as solidified glands, acinar formations, groups of cells, and as single cells. Many of the single cells and cells of the small groups were transformed into typical signet-ring cells with a drop of mucin in the center (Fig. 3). Many cysts contained epithelial cells floating freely within the mucinous contents of the cyst; these frequently were of the signet-ring appearance. In other sections of the ovary, small cysts, up to 15 mm. in diameter, were seen to be surrounded by a dense layer of fibrillar connective tissue which was invaded by epithelial downgrowths from the epithelium lining the cyst. With the mucicarmine stain it was shown that all the cysts were filled with large quantities of partially retracted mucin (Fig. 4).

The left ovary showed a marked fibrosis of the stroma which contained a few corpora candicantia. The albuginea in one area contained a few surface epithelium

inclusion cysts which were lined by a low cuboidal epithelium and filled with a seromucinous fluid, and surrounded by a dense frame of collagenic fibrils. No evidence of tumor tissue was seen.

Slides of the anterior fundic wall of the uterus revealed the myometrium to be markedly fibrotic and the demarcation line between endometrium and myometrium was jagged. A marked increase in perivascular connective tissue was present around the larger blood vessels. Beneath the serosa cystic and solid deposits of the carcinoma could be seen to invade the superficial layer of the myometrium (Fig. 5). In some of the cystic deposits many epithelial cells contained droplets of secretion, thus gradually transforming themselves into signet-ring cells. In between the tumor aggregates old blood pigment within histiocytes could be seen.

Sections of the omentum (Fig. 6) showed large areas of fat separated by dense vascular connective tissue septa. These septa were riddled by large and small cysts, glandular structures, small solid acini, and even single cells of a low columnar epithelium. These cells, especially those lining the larger cystic cavities, produced

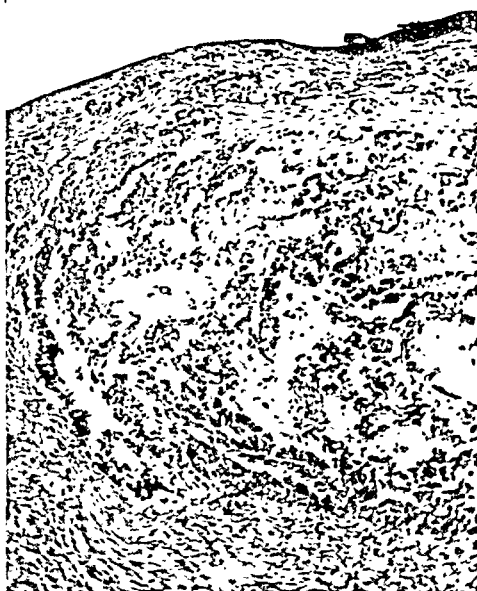


Fig. 5.

Fig. 5.—Deposits in the myometrium beneath serosa of uterine fundus.



Fig. 6.

Fig. 6.—Deposits in the omentum.

large quantities of a thick mucin. Some of the single isolated cells were transformed into classical signet-ring cells by the production of a central intraprotoplasmic drop of mucin. Small interstitial hemorrhages were occasionally seen within the field of carcinomatous deposits.

Several sections of transverse colon and its adjoining mesentery revealed an extensive replacement and separation of muscle cells by tumor deposits which were continuous with similar tumor masses within the mesentery. The mucosa was everywhere intact and uninvaded. The tumor deposits in some areas were cystic, in others glandular, and in still other areas infiltrating as solid clusters or single tumor cells. The cells everywhere showed an abundant mucin-staining cytoplasm, and in the case of the isolated cells, were frequently of the signet-ring shape. Within the mesentery itself the tumor aggregates were separated by very thick layers of edematous connective tissue.

A section of jejunum through the subserosal tumor nodule revealed a tumor deposit identical to that which has already been described but not invading the intact mucosa.

Sections of the gall bladder revealed a much thickened wall, largely replaced by dense fibrous tissue with frequent areas of hyaline degeneration. No tumor cells were seen.

Sections of the liver showed changes compatible with severe parenchymatous degeneration and passive congestion. No tumor deposits were seen within the liver.

DISCUSSION

The tumor in the ovary where it infiltrates the stroma by small groups and by single cells duplicates the so-called Krukenberg structure. The small cystic cavities, too, as far as they are round or slightly oval, fit into the picture of a Krukenberg tumor. They are frequently found combined with infiltrating signet-ring cells in ovarian deposits of primary intestinal carcinomas. Microscopic size cystic cavities, composing by themselves alone large ovarian tumors, have been described by Pfannenstiel as an entity and called "parvilocular cystoma." However, it is possible that this tumor of Pfannenstiel's is not an entity within itself but a special subgroup of the Krukenberg tumor. There is a close relationship between certain areas of some Krukenberg tumors in which the tumor forms microscopic small cysts, and the tumor which was described by Pfannenstiel. The tumor described by Pfannenstiel is very rare and since publication of his first cases in 1908 only a few more have been added to the literature.

In our case, in some areas the lining epithelium of the small cystic cavities shows adenopapillary projections which are not found in the typical Krukenberg tumor. These findings would tend to place the tumor into a relationship with the adenopapillary pseudomucinous cystoma. However the latter tumor has larger cavities, thinner septa, produces more mucin, and its cells have very little tendency to change into signet-ring cells; neither in the benign form when they float free in the mucinous secretions of the cysts, nor in the malignant form when they do the same or when they invade the stroma.

The subperitoneal deposits similarly duplicate by their adenopapillary projections the adenopapillary pseudomucinous cystoma, and by their tendency for signet-ring cells, the Krukenberg tumor. It has to be admitted that the presence of signet-ring cells in the subperitoneal metastases is less characteristic here of Krukenberg tumors than their presence in the ovary.

The unilateral development of this tumor, the small size, and the rather moderate increase in interstitial connective tissue, too, differ from the picture of a typical Krukenberg tumor, as well as the progressive peritoneal involvement which is found in only a few typical Krukenberg tumors. In the majority of cases the peritoneum is free and the propagation of the tumor from the primary site to the ovary does not occur by gravity through the peritoneal cavity, but as Jarcho and others have emphasized, by retrogressive lymphatic flow. On the other hand, direct proof cannot be given that the tumor originates from the ovary;

only by exclusion, since accurate gross and microscopic examination eliminated any other primary focus. The interpretation of this tumor as a primary endothelioma of the peritoneum, in the manner of explanations used for similar cases twenty to thirty years ago, is not in accordance with our modern conception of endotheliomas. Papillary projections and mucin production are characteristics which we do not like to attribute to peritoneal endothelium or its neoplasms. At least the origin of such tumors from the peritoneum has never been proved, although, for example, in ectopic pregnancies the peritoneum of the Fallopian tube and broad ligament may produce papillary projections of high columnar cells and a sort of mucoid secretion.

Concerning the origin of primary Krukenberg tumors, Novak and Gray have suggested tracing them back to teratoid inclusions. This seems likely, and we may be successful some day in finding a case of primary Krukenberg tumor which still shows the residue of teratoid tissue. Our case shows by its adenopapillary structures a certain relationship with the pseudomucinous cystoma; by its infiltrating signet-ring cells a close relationship to the Krukenberg tumor. However, since Robert Meyer has definitely proved that some pseudomucinous cystomas develop from the intestinal portion of teratoid ovarian inclusions, there is a possibility of linking a primary Krukenberg tumor like ours with the pseudomucinous cystoma of teratoid origin.

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Halbrecht, J.: Fresh and Stored Placental Blood, Lancet 2: 1263, 1939.

The author reports on the use of placental blood, stored up to fifteen days, in 220 transfusions. Blood from 5 to 6 placentas was used for each transfusion. Reactions, all mild, were observed in 5 per cent but were no more frequent than with fresh adult blood. The only chemical change of importance due to storing of blood was glycolysis increasing from day to day. There is a complete disappearance of granulocytes after the seventh day. The total white blood count decreases by the fifteenth day to 4,000-5,000 per c.mm. The erythrocytes are in general well preserved, and their power to combine oxygen is maintained. Slight hemolysis appears after several days of storing but almost never amounted to more than 1 per cent up to the tenth day. Quantities of free hemoglobin up to 710 mg. per 100 cm. (5 per cent hemolysis) do not seem to produce any undesirable effect.

CARL P. HUBER.

A STUDY OF PELVIC MEASUREMENTS IN 550 SOUTHERN WOMEN

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MENGERT¹ reported recently that the average pelvic measurements of 4,144 Iowa women agreed closely with those given by Williams.² For a long time we have had the clinical impression that the measurements for women in this area were much smaller than those given in textbooks,² and this apparent difference in size stimulated us to study the average pelvic measurements in a series of southern women.

In the past few years many changes have taken place in the conception of the shape of the average normal pelvis. Greulich and Thoms³ found that only 31.9 per cent of adults had the type of pelvis (gynecoid) which, according to anthropologic literature, is proper for white women. A comparison of the average measurements of the women of our series with those of Iowa led us to believe that some revision of the concept of size and measurements which are considered to be normal for the female pelvis should be made. We feel that measurements which would be normal for one group in the United States are not necessarily typical and normal for the average pelvis in another section of the country.

Five hundred and fifty women from the Touro Infirmary Clinic and the Touro-Tulane Clinic who were delivered between January, 1939, and January, 1940, were studied as to measurements and weights at term, type of delivery, and size of the baby. The average measurements were as follows: interspinous 23 cm., intercrestal 26 cm., external conjugate 18.5 cm., biischial or transverse outlet 7.9 cm., and 44 per cent of the diagonal conjugates could be reached. Each of these external measurements is 2 to 3 cm. smaller than those of Williams' series (see chart), and with the exception of the biischial is 2 to 3 cm. smaller than the Iowa women. Mengert found the average transverse of the outlet to be 9.3 cm., while the average for women in this area is 7.9 cm.

TABLE I

	TOURO	WILLIAMS	IOWA
Interspinous	23.0	25	25.5
Intercrestal	26.0	28	28.0
External conjugate	18.5	21	19.6
Diagonal conjugate	44% reached		22% reached
Biischial or transverse outlet	8.0 (7.96)	10.5	9.3

The method followed in this study was as follows: On the initial visit to the clinic the measurements were taken by the intern and checked by the resident. The transverse of the outlet and diagonal conjugate

were then checked by a staff member. When the patient had reached the eighth month, the measurements were checked again by the resident and the staff member, with special attention to the diagonal conjugate and transverse of the outlet. Thus in most cases the diagonal conjugate and transverse of the outlet were checked six times before the patient was delivered. We feel that the measurements are dependable and accurate to 0.5 cm. To check further the impression that pelves of southern women are small and to check the accuracy of our measurements, we measured a small number of pelves used by the students in anatomy. These pelves come from indigent patients of this area and should be representative. A few x-ray plates were also checked and found to be in line with the clinical measurements.

RESULTS

The External Conjugate.—The external conjugate or Baudeloque's diameter was found to be 18.5 cm. In Williams' series² this figure was 21 cm. and in Mengert's series¹ 19.6 cm. Williams² states that "an external conjugate of 18 to 19 cm. is a danger signal" of contracted internal diameters. This could not hold in this series, since 18.5 cm. is our average, and since 72 women (13 per cent) had an external conjugate of 17 cm. or less and had no internal contraction.

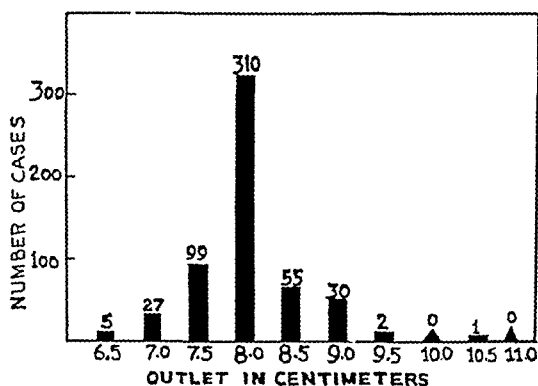


Fig. 1.—Transverse diameter of outlet. 441 cases, or 83 per cent, were 8 cm. or less; 32 cases, or 6 per cent, were 7 cm. or less, considered as contracted outlet.

The Transverse of the Outlet.—The normal biischial diameter or transverse of the outlet is given by Williams² as 10.5 to 11.0 cm. Not a single transverse of the outlet of 11.0 cm. was seen in this clinic in the past year. Only one woman had a transverse of the outlet of more than 9.5 cm.; 30 women had a transverse of the outlet of 9 cm., in 55 women it measured 8.5 cm., in 310 (or 60 per cent) 8 cm., in 99, 7.5 cm., in 27, 7 cm., and 5 negroes had a transverse of the outlet of 6.5 cm. or less (Table II). No white woman had a transverse of the outlet of less than 7 cm. Williams states that "whenever the transverse diameter of the outlet measures 8 cm. or less we designate the pelvis as funnel" and he noted 6 per cent of funnel pelvis in 10,000 cases. On this basis our incidence of "funnel pelvis" would be 83 per cent, or 441 cases out of 529. It is a common observation that outlet dystocia is very rare, and we agree with this. We have had no difficulty with outlets of 7.5 cm. of which we had 99 in this series. A patient with an outlet of 7 cm. requires careful watching and a larger episiotomy to avoid damage to the perineum and rectum, but we have seen no true dystocia result. The posterior sagittal should always be measured in these cases. We feel that a transverse of the outlet of 8 cm. should not be the standard for a funnel pelvis in southern women, but that 7 cm. should be considered borderline and 6.5 cm. or less should indicate a true funnel pelvis for women in this area. Using these standards our incidence of funnel pelvis is 6 per

cent (see Fig. 1). (Note: We do not routinely measure the anterior posterior diameter of the outlet and posterior sagittal, so these figures were not submitted to analysis. The posterior sagittal, as noted above, is measured when the biischial is 7.5 cm. or less.)

The Diagonal Conjugate.—The majority of women came to the clinic in early pregnancy and the pelvic measurements were checked then, as well as at the eighth month, at which time special effort was made to reach the diagonal conjugate measurement. In 44 per cent the promontory could be reached as against 22 per cent in Mengert's series which is again in line with evidence that the pelves of southern women are smaller than those of women in other areas (Figs. 2 and 3).

More concrete evidence of the small size of the pelves of southern women can be deduced from the x-ray studies of Torpin and Holmes⁴ of the University of Georgia. They measured the inlet of 400 women, divided the pelvic types into 4 groups, and then showed the number of cases in each group with different lengths of conjugate vera. We find that if we add from 1.5 cm. to 2 cm. to each conjugate vera we have the approximate diagonal conjugate in their series. Torpin's and Holmes'

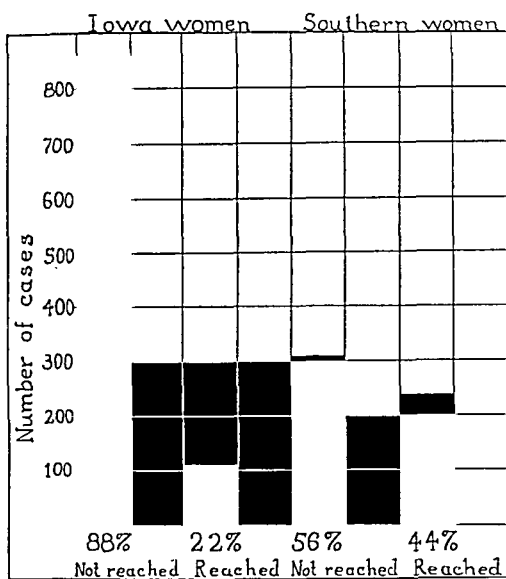


Fig. 2.

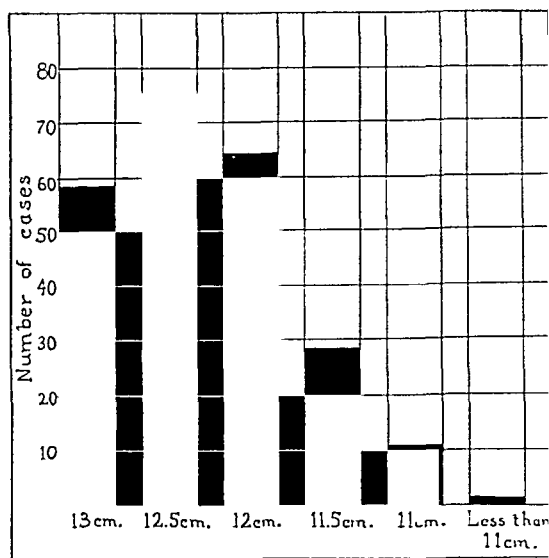


Fig. 3.

Fig. 2.—Sacral promontory not reached in 88 per cent of Iowa women. Sacral promontory not reached in only 56 per cent of southern women.

Fig. 3.—Slightly less than half (44 per cent) of the diagonal conjugates could be reached. One hundred and ninety-eight of the 240 diagonal conjugates reached measured between 12 and 13 cm.

findings agree with our clinical determinations, as 88 per cent of their diagonal conjugates would be 13 cm. or less, and 60 per cent to 70 per cent of these could probably be measured clinically. Only 12 per cent of diagonal conjugates in their series were more than 13 cm. as obtained by addition of 2 cm. to x-ray conjugate vera (Table II).

TABLE II

	CONJUGATE VERA IN CM. MEASURED BY TORPIN					
	6-8.5 cm.	9 cm.	10 cm.	11 cm.	12 cm.	13 cm.
Converted to diagonal conjugate (2 cm. added)	10.5 cm. or less	11 cm.	12 cm.	13 cm.	14 cm.	15 cm.
Cases total 400	6	36	148	163	39	8

88 per cent had a diagonal conjugate of 13 cm. or less, and 60 per cent could probably be reached clinically.

RACIAL DIFFERENCES

Many statements have been made regarding racial differences in pelves, especially as regards white and colored patients. Some local physicians also expressed the belief that the reason for the apparent smallness of the female pelvis in New Orleans was because the majority of women came from Latin stock and were small in stature. So the clinic patients were divided into 3 groups for study as follows: 137 "Latins" made up of women of French, Spanish, and Italian descent; 170 "Anglo-Saxons" of English, Irish and German descent, and a third group of 238 negroes. As shown in Table IV the measurements of each group are surprisingly similar to the others. The measurements were practically identical for the diagonal conjugate, transverse outlet, and external conjugate diameters, while only the interspinous varied as much as 1 cm. from the general average (Table III).

TABLE III

	ANGLO-SAXON	LATIN	NEGROES	TOURO ALL GROUPS
Interspinous	23.24	24.2	22.3	23.0
Intercrestal	26.4	26.4	25.75	26.0
External conjugate	18.28	18.28	18.7	18.5
Diagonal conjugate	41%	40%	48%	44% reached
Biischial or transverse outlet	7.9	7.9	8.0	8.0 (7.96)

There is no marked difference in the size and shape of the negro pelvis and the pelvis of the southern white woman as is described by some northern writers.⁵ Neither have we noticed the presence of rickets (or the contracted "rachitic pelvis") which is said to be common in the negroes living in the North.

This was mentioned by W. E. Levy,⁶ in 1926, who compared 500 negro women and 500 white New Orleans women from an obstetric viewpoint. He included pelvic measurements as a part of his study and found "very little difference in the pelves of the two races except in two of the external measurements." His measurements were practically the same as those found in this study, varying no more than 0.4 cm., but he made no comparison of these figures with pelves of northern women.

The average weight for women of Anglo-Saxon descent was 143 pounds at term, for Latin women 144 pounds, and for negro women 146 pounds. The average weight of the whole group at term was 145 pounds. This is probably smaller than the average for women of Scandinavian descent at term, but we have no proof of this. The negroes weighed more at term because most of these patients in our clinic are multiparas and are from a higher age group, while the white women are more than 90 per cent primigravidas.

INCIDENCE OF CONTRACTED PELVIS

As stated above, 83 per cent of outlets were 8 cm. or less, and this would be the incidence of funnel pelvis according to Williams' standards. But taking 7 cm. or less as our standard for funnel pelvis, our incidence is 6 per cent. We had 27 patients with outlets of 7 cm. and all delivered

without difficulty with low forceps plus episiotomy which is routine in our clinic for primiparas. Five women (all negroes) had an outlet of 6.5 cm. or less. Two of these, with small babies, delivered from below. The other 3 with outlets of 6.5 cm., 6 cm. and 5.5 cm., respectively, were delivered by section, because the babies were rather large.

Fourteen women (2.6 per cent) had inlet contractions (Table III). Twelve had a diagonal conjugate of 11 cm. and 2 had a diagonal conjugate of 10.5 cm. Both women with diagonal conjugates of 10.5 cm. were delivered by section. One of these two also had an outlet of 6 cm. One patient with a diagonal conjugate of 11 cm. who had had two previous sections was delivered by cesarean section. One woman with diagonal conjugate of 11 cm. had a Porro section after a long difficult labor and Bandl's contraction ring (fetal death). Another patient with a diagonal conjugate of 11 cm. had a transverse arrest and was delivered of a 9-pound male by midforceps plus episiotomy, followed by shock from hemorrhage. The remaining 10 women with diagonal conjugates of 11 were delivered with comparative ease by low forceps and episiotomy. Three other women with apparently average measurements for our general group required cesarean section during the year; 2 for cephalopelvic disproportion and one for previous section. Twelve sections were done in a group of 550 women delivered from January, 1938, to January, 1939, for "all indications"; an incidence of 2.2 per cent. Eight of these sections were done for cephalopelvic disproportion, an incidence of 1.4 per cent. No versions were done and only 21 midforceps were done, an incidence of 3.8 per cent. There were 8 stillbirths during the year, an incidence of 1.4 per cent. Three of these fetal deaths, however, were due to prematurity so that the corrected mortality of term infants was 0.9 per cent.

TABLE IV

			SEC- TIONS	MID- FORCEPS	VERSION	BREECH EXTRAC- TION	LOW FORCEPS AND EPISI- TOMY	SPON- TANE- OUS
All cases 550			12	21	0	27	222	268
Contracted pelves 46	Inlet	14	3	1	0	0	10	0
	Inlet and outlet	1	1	0	0	0	0	0
	Outlet	31	2	0	0	0	29	0

There were two maternal deaths during the year; neither patient was operated upon. The first patient had pyelonephritis and delivered a premature infant precipitately without internal examination. She died in three weeks with a staphylococcal septicemia. The other patient, a negro, had tuberculosis and died in labor. Autopsy showed Pott's disease and a psoas major abscess.

If southern women have smaller pelves than northern women, the question of the relative size of the babies arises. Williams² gives 7½ pounds as the average weight of full-term babies. In our series we found the babies of Latin mothers to average 7.36 pounds, those of Anglo-Saxon 7.41 pounds, and the negro babies weighed 7.61 pounds. Most of the negro patients were multiparas; this accounts for the larger size of the babies in this series. The average of the whole group was 7.53 pounds which agrees with the figures given in most textbooks. Thus it appears that southern women deliver average-sized babies through pelves the minimum diameters of which are somewhat smaller than the measurements given in the majority of American textbooks.

SUMMARY AND CONCLUSIONS

1. We believe that the obstetrician should know what is the typical normal pelvis in his particular section of the country.

2. The average measurements in 550 southern women were found to be interspinous 23 cm., intercrestal 26 cm., external conjugate 18.5 cm., biischial 8 cm., and 44 per cent of diagonal conjugates could be reached.

3. Only an average transverse of the outlet of 7 cm. or less should be considered as diagnostic of funnel pelvis.

4. We are of the opinion that in the past many patients in this area have been subjected to cesarean section without a trial of labor because of a supposedly contracted pelvis when in reality the measurements were the average for women in this section.

5. Since a larger group of southern women have small pelves, our operative incidence and incidence of section could properly be higher than in some other locations. The figure is 1.4 per cent, which is not high, and the authors feel that more mistakes have been made in denying patients section than in being radical.

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A CLINICAL STUDY OF THE INCREASED RESPONSE OF THE FULL-TERM GRAVID UTERUS TO PITUITRIN AFTER ALKALINIZATION

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SCIENTISTS have theorized and rationalized from the earliest times concerning the causes of labor. Chemical and endocrine studies have been undertaken, both in animals and in man, and many probable predisposing factors for the normal onset of labor have been promulgated but nature still hides the secret of the exciting cause.

It does seem, at present, that a certain something develops in the blood which either brings on labor itself or so sensitizes the uterus that a substance, normally present, has an oxytocic effect. For instance, Jeffcoate¹ has shown that estrin is essential for all uterine contractions in vivo; and since, in its absence, coordinated contractions do not exist, it may be postulated that the presence of estrin is a necessary condition for labor. But this does not mean that estrin acts alone in the causation of labor. Its presence increases most remarkably about the fifth month of gestation and, although it rises gradually until term, there is no significant change at that time which would initiate the violent contractions of labor.

Beginning with Hippocrates, many obstetricians and midwives have noticed that certain changes in the weather may precipitate labor in groups of patients. Women themselves believe in the tradition that a storm might bring on the pains. DeLee refers to it. We have observed that births seem to occur in groups, with interval lulls, and were, therefore, led to a study of the influence of meteorologic events on labor pains. This work, unpublished, analyzed the occurrence of over 16,000 births in St. Louis in 1937 and showed that a preponderance were associated with the passage of cold air masses.

If meteorologic stimulation of the organism is a fact and the onset of labor can be traced to changes in the meteorologic environment, other changes should be measureable in rhythmic shifts which coincide to changes in the weather chart.

Petersen,² in an extensive study, observed, in detail, changes in the blood pressure, serum proteins, blood pH, carbon dioxide-combining power, blood electrolytes, and basal metabolic rate which occur as a result of certain weather mixtures. He has shown that the passage of a cold air mass results in smooth muscle spasm and corresponds, in general, to sympathicotonia. His studies reveal an increased blood pH and carbon dioxide-combining power coinciding with these so-called cyclonic fronts of the weather.

Reasoning from the results of our study which showed an increased number of births during this type of weather, we believe that the increase in the body's alkalinity at this time could be considered as the necessary unknown quantity that conditioned the individual for labor.

In brief, it has been demonstrated, statistically, that the distinct periodicity in the precipitation of labor is to be related to the passage of a cold air mass and that this phase, besides manifesting itself in smooth muscle contractions, is a definitely alkaline phase.

ACID BASE BALANCE OF THE BLOOD DURING PREGNANCY

Examination of the literature on the subject of acid-base balance during pregnancy reveals a maze of confusing and contradictory observations.

Nice and others³ and Oard and Peters⁴ report a compensated alkali deficit while Meyers and Muntwyler⁵ and Dieckmann and Wegner⁶ show evidence which indicates that the change, if any, is toward the alkaline side. Unfortunately, we have no determinations, as far as I can find in the literature, taken in series, during the period that immediately precedes the onset of labor. I believe we would find an alkaline preponderance at this time, since labor is most commonly precipitated on the barometric highs and on the cold fronts when there is a greater tendency to spasm and relative blood alkalosis.

Apart from the factor of alkalosis, certain other pertinent references in the literature are worthy of our consideration here. Kochman and Kruger,⁷ studying puerperal human uteri, found a decided change in the potassium-calcium ratio of this tissue over the ratio in the normal uteri, there being an increase in the potassium and a decrease in the calcium. Heller and Holtz,⁸ in experiments with isolated guinea pig uteri, found that this shift greatly augmented the sensitivity of the uterus to pituitrin. Knaus and Clark,⁹ likewise, have demonstrated that an increase in calcium caused a definite diminution in uterine tonus.

I mention the works of these investigators because of the importance they attach to the effects of these two elements on the sensitivity of the uterus and because there occurs a decidedly similar shift of these two elements during a period of maximum alkalosis. The decreased ionization of calcium in the swing to the alkaline side can be explained by the fact that calcium is insoluble in alkali and soluble in acid, and that it is mobilized from the bones in acidosis and returned to the bones by alkali.

A NEW METHOD FOR THE MEDICAL INDUCTION OF LABOR

With the idea of testing the thesis that the human gravid uterus is relatively more sensitive to pituitrin after complete alkalization of the patient, 94 medical inductions were attempted on the alkalized patient and the results compared with 113 inductions carried out according to the usual Mathieu¹⁰ technique, and with 20 who were acidified, as controls.

These patients were selected at random from the Obstetric Clinic at Firmin Desloge Hospital with only one criterion prerequisite, i.e., the patient be at term.

All of these patients were either given 40 Gm. of sodium bicarbonate or 60 Gm. of Upjohn's "citrocarbonate," in divided doses, beginning the day before the attempted induction.

A study of the alkaline reserve was made before and after the ingestion of the bicarbonate by means of the carbon dioxide combining power determinations and urine pH changes. Blood pressure changes and side effects of the medication were also recorded. The intensity and number of uterine contractions were not measured by any definite standard, the only criterion for success or failure of the method being whether or not the patient went into labor after the injection of the pituitrin. After alkalization, these patients were given a hot soap solution enema followed immediately by two-minim doses of pituitrin at twenty-minute intervals for a maximum of eight doses or until labor was established. Not infrequently only one or two doses of the pituitrin was necessary in order to initiate labor.

Side effects of the medication were practically nil. Most of the patients referred to a frequency of bowel movements but only two complained of vomiting the bicarbonate. In these cases, the dose was repeated at once. There was no evidence of fetal apnea or delayed respiration. Changes in the blood pressure were remarkably absent.

The carbon dioxide-combining power was raised an average of 14 volumes per cent by the alkali, and ranged in individual cases from a 6 to a 21 volumes per cent rise.

The urine pH varied from 6.5 to 9.0 after the bicarbonate and, in the majority of cases, was raised from 6.5 to 9.0.

Of the 94 inductions attempted, 65 succeeded, giving an efficiency of 70 per cent to the method.

In the control group, who were not alkalized, there were 46 successes out of 113 attempts, or an efficiency of 44.6 per cent.

SERIES OF 20 PATIENTS MEDICALLY INDUCED AFTER ACIDIFICATION

Because of the establishment of the preceding facts, we can anticipate as a necessary corollary, that the gravid human uterus, after acidification, shall be relatively less responsive to pituitrin. Reasoning thus, we attempted twenty inductions after acidification with ammonium chloride.

The first 12 of this series received 4 Gm. of ammonium chloride daily for three days and were then subjected to an induction of labor identical to that in the alkaline series. Because we were unable to obtain a urine pH lower than 5.5 under this regime, the ammonium chloride dosage was increased to 6 Gm. daily on the remaining 8 patients.

The patients suffered no subjective symptoms referable to the acidosis.

The average figure for the alkaline reserve of these patients, after acidification, as studied by the carbon dioxide-combining power, was 46 volumes per cent. Compared with the average of 66 volumes per cent for the patients who were alkalinized, this shows a difference of 20 volumes per cent between the two series.

The urine pH averaged 5.5 for the 20 cases but ranged from 4.4 obtained in 5 cases to 7.2 obtained in 1 case. Of the 20 inductions only 3 succeeded, giving an efficiency rate of just 15 per cent to the method.

None of the attempted inductions was made before maturity. In fact, most of the cases were ideally suited for a successful induction, inasmuch as the fetal head was engaged in all cases and the average McDonald measurement was 36 cm. In no case was induction attempted with a McDonald below 34 cm.

TABLE I. SHOWING RESPONSE OF UTERUS TO PITUITRIN AFTER ALKALINIZATION, ACIDIFICATION AND MATHIEU TECHNIQUE OF INDUCTION

INDUCTIONS	NO. ATTEMPTED	NO. SUCCEEDING	PER CENT SUCCEEDING
After alkalization	94	65	70.0
After acidification	20	3	15.0
According to Mathieu ¹⁰ technique	113	46	40.7

According to our experience with the original Mathieu technique, we have been unable to produce the high percentage of successful results claimed for it and have, therefore, sought a safe and more efficient method for the medical induction of labor. We firmly believe that the method of alkalinizing the patient before attempting the induction has produced, by far, the most satisfactory response of any heretofore published technique, excluding, of course, the various mechanical means with their attendant disadvantageous dangers.

It should be again emphasized that this series of inductions of labor, attempted after alkalinization, represents a group selected at random from the dispensary for the only reason that the patient had reached or passed her calculated term of gestation. The height of the uterus, engagement of the head, and thinning of the cervix were ignored. I feel that had we selected cases with deep engagement of the head and beginning effacement of the cervix our results would be even more impressive.

SUMMARY

Believing that there is a definite need for a more dependable technique of the medical induction of labor, and failing to achieve this end by utilizing the heretofore accepted routines, we have rather deviously hit upon a method, indirectly reached as a result of a previous study correlating the incidence of births with weather changes.

It is difficult to draw definite conclusions from a small series of 94 cases, but I believe that there lies here, at least, the nucleus of a theory suggesting the following:

1. The gravid human uterus, in vivo, responds more favorably to pituitrin after alkalinization.

2. Forty grams of sodium bicarbonate or 60 Gm. of "citrocarbonate," by mouth, in doses divided over a period of twenty-four hours, is an efficient alkalinizing agent.

3. Side effects of the medication are practically nil.

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4500 OLIVE STREET

TREATMENT OF POSTERIOR FACE PRESENTATIONS

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ALL reported studies of posterior face presentations have stressed the danger of this position to both mother and child. Reed¹ reported a maternal mortality of 11.6 per cent and a fetal mortality of 40.6 per cent. Recent statistics are lacking, but the predominant feeling is well summarized by De Lee² who concludes that "mentosacral positions terminating happily for the mother and child are so exceedingly rare that for practical purposes it is best to consider them as absolutely impossible and as always requiring interference from art." Taylor³ and Penrose⁴ as well as Reed long ago debated the absolute necessity for interference and quoted instances of spontaneous delivery of living infants. But they agreed that failure to rotate or advance was a definite indication for assistance.

Since Baudelocque⁵ advocated manipulation in the treatment of face positions there has been much discussion regarding the necessity for such interference. Unanimity is not yet absolute but leading authorities agree that many anterior face presentations can be left to nature, intelligently supported. This policy has proved satisfactory on this service with the occasional assistance of low or midforceps.

The patients on whom this summary is based were treated on the maternity service of the Metropolitan Hospital, New York City, under the direction of Dr. H. E. Ayers. Treatment in each case followed individual consideration. Internal manipulations were performed under general anesthesia. The procedure used was dependent on the stage of labor at the time of discovery as follows:

A. Before the onset of labor (this occurred only once) the position was corrected successfully by the abdominal maneuver described by Schatz⁶ in which the infant's chest is pushed strongly towards the occiput and up, while the breech is pulled in the opposite direction, automatically elevating and flexing the head. The diagnosis was corroborated by x-ray before and after correction. Occiput-anterior delivery occurred spontaneously two weeks later.

B. After the onset of labor: 1. With the cervix 2 fingers dilated, the combined internal and external maneuver described by Ziegenspeck⁷ was used. Two fingers were inserted through the cervix disengaging the face and progressively flexing the head while an assistant used the "Schatz" maneuver to re-align the body. This was attempted once only in Case 6 and the position corrected but not maintained. A brow presentation without descent later resulted. Because of a borderline contracted pelvis in addition to good condition of mother and child, a trachelolaparotomy was resorted to with satisfactory results to both.

2. With the cervix three or more fingers dilated, the face was pushed up and the head flexed and guided into occipito-anterior position by the internal hand, while the external hand flexed the body and maintained fundal pressure as described by Thorn.⁸ This was attempted in five cases and was successful in four. Spontaneous delivery followed in three, and the fourth was terminated by mid-forceps. All these infants survived and apparently were normal on discharge from the hospital.

3. With full dilatation of the cervix and a contracted uterus: The Thorn maneuver was attempted unsuccessfully in one such case (Case 3). This patient was then treated by manual rotation of the chin anteriorly and forceps delivery as a mentum anterior. Another patient (Case 2) was similarly treated by rotation anteriorly and forceps delivery, but without attempted conversion to occiput presentation. These were the two babies that did not survive the neonatal period, succumbing on the fifteenth day and after the sixth hour, respectively. Autopsies were obtained on both. The first confirmed the clinical impression of cerebral hemorrhage. The second occurred unexpectedly, and there were no definite internal abnormalities except cerebral edema.

4. The long neglected case in which the chin becomes impacted in the hollow of the sacrum, with the forehead still above the symphysis pubis is becoming less frequent. However, when it does occur the outlook is still very bad. Hebosteotomy,⁹ craniotomy, and version are variously recommended, but all have serious objections and are certainly not ideal for all such cases. With this in mind, we believe the following case (Case 7) to be of unusual interest as it is to our knowledge the only report of a successful delivery from an impacted posterior face position by an extraperitoneal cesarean section. This choice of operation was guided by: (1) the long labor with ruptured membranes, (2) the tight uterus with a definite contraction ring, (3) small pelvis, and (4) the good condition of mother and child.

The operative technique followed was that recently developed and admirably described by Waters.¹⁰ In addition to the logical simplicity of this extraperitoneal approach, the site of the low transverse uterine incision is ideal for the delivery of the hyperextended occiput, albeit some difficulty may be expected from the tightly contracted uterus.

Case History (No 10797).—(Case 7.) The patient was a young single primigravida of eighteen years admitted on March 17, 1940, three weeks before her estimated date of confinement. Pains had begun, however, three days before admission. Rupture of the membranes had occurred the day previously and for twelve hours there had been bearing down pains. The previous history was irrelevant and the ante-partum course had been normal. She had attended the antenatal clinic and no abnormalities had been noted on her last visit two weeks before admission.

The patient's general condition appeared good except for coryza and congested nares. Heart and lungs were normal. Pulse was 90 and blood pressure 122/90. The temperature was 99.4° F. The uterus seemed full term with the fundus 2 fingers below the xiphoid. Contractions were strong every three minutes. On the left suprapubically was a large cephalic prominence and just above was a persistent contraction ring. The fetal heart was regular, in the R.L.Q., with rate of 150. The uterus was tetanic. Over the vulva a bloody mucoid discharge was present. On rectal examination several irregular bony protuberances were felt with the mouth apparently posterior.

On vaginal examination the cervix was found fully dilated and retracted. The presenting part was the full face, edematous and bulging just below the spines. The chin was posterior and slightly to the right. No membranes could be felt. The chin was fixed and could not be dislodged upward or rotated anteriorly by firm pressure. The pelvic concavity was small with a deep sacral hollow. The promontory was hidden by the chin. The diagnosis was an impacted face presentation in the right mentum posterior position in second stage labor. X-rays confirmed the diagnosis and revealed a small inlet with an android posterior segment. External measurements were: interspinous, 20.0 cm.; intercrystal, 23.5 cm.; external conjugate, 19.0 cm.; bischial, 8.0 cm.

Because of the long labor with ruptured membranes (more than sixty hours), lack of descent on bearing down, Bandl's contraction ring, small pelvis, fixation of face and good condition of mother and child, a supravescical extraperitoneal cesarean section was decided upon. The operation started at 2 P.M., March 17, 1940, and was conducted under spinal anesthesia, 120 mg. procaine and $\frac{1}{2}$ c.c. of 1 per cent pantocaine. The operating time was sixty-five minutes.

Procedure.—A low left paramedian incision was made over a filled bladder and carried through skin, subcutaneous tissue, superficial and deep fascia, muscle separated easily, bleeding controlled with ligation. Transversalis and perivesical fascia were incised in midline down to bladder wall. Upper angle of this incision extended transversely across bladder below peritoneal reflexion. Perivesical fascia was elevated off bladder and pushed laterally by blunt dissection. Vesicouterine fold of fascia was identified in left upper angle and cut. Bladder was emptied, and this incision extended across fundus of bladder, thus cutting off vesicouterine fascial attachment to bladder and allowing latter to drop well down. Bleeding was controlled with ligation. Peritoneal fold retracted upwards. Uterine fascia incised transversely, and pushed up and down, thus exposing all of lower uterine segment. Contraction ring was identified. Upward curved transverse incision was made through uterine wall just below this contraction ring, vertex presenting in opening. Child delivered with vectis and fundal pressure. Ergotrate 1 c.c. given intravenously. Uterine wall was closed with two layers of continuous chromic gut No. 2. Peritoneal flap was pulled down intact over bladder. Penrose drain was inserted behind bladder in uterovesical space. Three heavy dermal tension sutures were placed. Fascia was closed with continuous chromic No. 2 catgut, interrupted around drain. Skin was closed with black silk interrupted vertical mattress sutures.

A normal male child, weighing 7 pounds, 5 ounces, was delivered and a normal respiratory rhythm was established after some difficulty. The hyperextension of the head gradually diminished during the first two weeks.

The blood pressure and pulse remained good throughout the operation, and there was very little postoperative reaction. The abdomen was always soft. Fluids were well taken and there was voiding spontaneously on the first postoperative day. Skin sutures were removed on the sixth day and tensions on the eleventh postoperative day. The patient was out of bed on the fourteenth and home on the seventeenth postoperative day. X-ray of pelvis post partum revealed an android type posterior pelvis with a converging fore pelvis. True conjugate diameter was 10.75 cm. (Thoms). Diameters of the fetal head at birth were: occipitofrontal 12.75 cm., and biparietal 10.0 cm. The patient was seen and examined the first and second months after discharge. Her general condition was good. The incision was well healed. The uterus was well involuted and in good position. There were no adnexal masses or bladder disturbances. The baby was healthy.

SUMMARY

The treatment of 8 cases of posterior face position in labor and of one before the onset of labor is described. The latter was converted to an occiput presentation by the abdominal maneuver of Schatz.

During labor four of these positions were converted by the Thorn maneuver to the occiput anterior and safely delivered. Two others were rotated to a mentum anterior and delivered as such with forceps. One patient was delivered by a low flap cesarean section, and one by a supra-vesical extraperitoneal cesarean section. There were no maternal deaths or stillbirths. The two infants delivered by forceps in the mentum anterior position died during the neonatal period apparently to the effects of birth trauma.

Version was not attempted in this series primarily because of (1) a contracted or borderline pelvis; (2) a tight, thin uterus with membranes long ruptured; and (3) an incompletely dilated cervix.

The etiology of this abnormal position was not always clear but one constant finding seemed to be relative disproportion between the size of the infant and pelvis. The pelvic asymmetry was demonstrated by the three small android pelvises which we were able to check by x-ray, and the fetal factor by one large eleven-pound child and by one small five-pound, twelve-ounce child in a large multiparous woman. Multiparity and relaxed abdominal walls did not seem to be important, as there were four young primiparas with firm musculature and only two had had more than two children. A differential between primary and secondary dolichocephaly could not be established, but it is interesting to note that of the 6 babies whose head measurements were recorded, 5 had an occipitofrontal diameter of 12.5 cm. or greater. The exception was the small child mentioned above whose occipitofrontal measurement was 9.5 cm.

Early diagnosis and accurate determination of size and shape of pelvis are essential to the proper conduct of this type of dystocia. X-ray pelvimetry is of assistance but not always conclusive. Where definite cephalopelvic disproportion exists, cesarean section is the method of choice, except that in the cases where labor is far advanced the choice lies between extraperitoneal section, hebosteotomy, and craniotomy.

In the borderline case, conversion to the occiput anterior is the safest course. If descent does not then follow, forceps delivery must be added to the three procedures mentioned in advanced cases. In patients with ample pelvises, spontaneous rotation to the mentum anterior is the rule. We believe that this explains the constant finding of small pelvises in this group of persistent posterior face presentations. This also raises the question of the advisability of rotation to the mentum anterior and forceps delivery in cases with relatively contracted pelvises. Extraperitoneal cesarean section and hebosteotomy are definitely less harmful to the infant.

CONCLUSIONS

1. Relative cephalopelvic disproportion is frequently found in posterior face presentations.

2. Manual conversion to the occipitoanterior position is feasible and is the safest form of delivery for both mother and child.

3. Version and extraction are contraindicated in many of these cases.
4. Forceps rotation to mentum anterior and delivery in this position resulted in high neonatal mortality.
5. Supravescical extraperitoneal cesarean section is a logical and practicable addition to the treatment of impacted posterior face presentations.

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THE TREATMENT OF GONORRHEAL SALPINGITIS WITH ESTROGENIC HORMONES

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GONORRHEAL infection of the adult female genital organs originates in the external genitalia. Skene ducts, Bartholin's glands, and the cervical glands are the sites of predilection of the infection. These depots of gonococci, especially in the cervical glands, constitute a steady menace to the Fallopian tubes. Invasion of the tubes takes place through a grass-like growth along the genital mucosa. An anatomic continuity of the mucosa for this purpose is indispensable.¹

Observation on a large number of patients showed that the primary attack of gonorrheal salpingitis occurred at the time of menstruation, while only few and comparatively mild cases were observed in the postpartum and postabortal periods.

The biologic and physiologic functions of the Fallopian tubes are governed to a great extent by the follicular hormones. The follicular hormones increase the peristalsis and other movements of the tubes (Reynolds, S. R. M.,² Geist, S. M., Salmon, U. J., Mintz, M.³), animate the ciliary motion of the columnar cells, stimulate the proliferation of the tubal mucosa (Novak, E., Everett, H. H.,⁴ Caffier, P.⁵), and promote the growth of the entire organ in case of infantilism (Clauberg, C.⁶). These effects in combination with others yet to be detected, add to the protective resistance of the tubes.

While one may attribute the relative scarcity of the gonorrheal-salpingitis attacks in the postgravid periods to the copious drainage and to the invasion of the uterine cavity by more potent germs; however, their mild character suggests an increased resistance of the Fallopian tubes to the gonorrheal infection at these times,

At the time of menstruation, the estrogenic hormone level drops and so the tubes are deprived of the beneficial action of the hormones, thus creating at menstruation a point of lowered resistance. Post-partum and postabortal, the drop in the estrogenic hormone level is not as drastic as at the time of the menstruation, and possibly the hormones of the involution substitute to some degree for the estrogenic hormones in the protection of the tubes against the gonococcic invasion. Therefore, it was believed that a maintenance of the follicular hormone level at the time of the menstruation might constitute a reasonable therapy in bridging over the "danger period." Furthermore, since proliferation and ensuing desquamation of the genital mucosa is the main weapon in the fight against a gonorrheal infection and since the estrogenic hormones stimulate this proliferation, an increase in the estrogenic hormone level in any phase of a gonorrheal salpingitis attack will be beneficial.

It was empirically estimated that 30,000 international units of follicular hormones, divided into three doses and given intramuscularly at the onset of menstruation would be sufficient for the bridging of the "danger period," while in the treatment of acute gonorrheal salpingitis, a daily injection of 10,000 international units was decided upon.

MATERIAL AND RESULTS

The above described treatment was instituted on Aug. 1, 1937. The patients were divided into two groups: Group I, patients with chronic salpingitis treated in the Out-patient Department of the Harlem Hospital; Group II, patients with acute salpingitis hospitalized on the wards.

Group I. Cases With Chronic Salpingitis.—To this group were admitted patients with one or more attacks of salpingitis, palpable adnexa or adnexal tumors, and abdominal discomfort. The conditions for admission were: normal temperature, sedimentation rate, and white cell count. These patients were treated with estrogenic hormones at the time of menstruation, and except for sedatives and vinegar douches, did not receive any other form of treatment.

Seventy-four patients were treated through 6 to 10 periods. Fourteen of these patients had been previously hospitalized for acute salpingitis. During the time of their treatment, there was no recurrence of salpingitis. Except for sporadic minor complaints, the patients steadily improved. Frequent gynecologic examinations disclosed a gradual decrease in the size of the adnexal tumors and in a large number of cases, complete disappearance. Two patients became pregnant.

A control group of 20 patients was treated for six months with distilled water injections instead of estrogenic hormones at the time of menstruation. Twelve patients showed a gradual improvement, 2 patients suffered an acute attack of salpingitis and 6 patients complained of stationary or increased discomfort and demanded a change in treatment.

Group II. Cases With Acute Salpingitis.—All these patients were hospitalized cases. They were divided into two groups:

Group A. Menstruating Group: To this group belonged patients who had their periods while hospitalized and were treated at this time with three injections of 10,000 international units of follicular hormones at three-day intervals. Fifty-four patients received such treatment. Seventy per cent of these cases had normal temperature during and after their periods, while 30 per cent continued to be febrile. In several instances, instead of the 10,000 international units, 3 times a week procedure, a daily injection of 4,000 international units was used and the results in these cases were slightly better than in the rest of the patients in the group. In a control group of 48 patients, who did not receive any treatment what-

soever, just the opposite results were obtained, i.e., 70 per cent of these patients continued to be febrile, and only 30 per cent had normal temperatures.

Group B: This group consisted of 37 patients whose attack of salpingitis did not follow a short term course and whose temperature remained constantly high despite the routine treatment. These patients were given injections of 10,000 international units of estrogenic hormones at daily intervals. While no percentual figures are claimed in these cases, the beneficial action of the injections was manifested by marked and occasionally dramatic improvement.

DISCUSSION

The only paper dealing with the treatment of gonorrheal salpingitis with follicular hormones was published in 1939 by Clauberg,⁶ who obtained beneficial action from the use of the follicular hormones in cases of chronic gonorrheal salpingitis. He ascribes this effect to hyperemia, proliferation of the mucosa, and especially to growth of the entire tube. Several reproductions of salpingograms with re-established patency of the tubes were shown. 50,000 international units at five-day intervals between periods in conjunction with other types of treatment such as baths, diathermy, and short wave were employed. In his opinion, the growth of the whole organ, with a simultaneous enlargement of the tubal lumen was regarded as the most important factor in the re-establishment of the patency.

The treatment described in this paper was instituted two years previous to the publication by Clauberg and is based upon a somewhat different point of view. The dosages are much smaller.

Synthetic and biologic hormones of different types were used with equally good results. No discomfort or noteworthy disturbances in the menstrual cycle were observed.

The depots of gonococci in the external genitalia were not treated on account of the experimental status of these cases. It was regarded as essential to maintain the threatening foci intact to prove the value of the follicular hormone therapy in the prevention of re-infection of the tubes.

Naturally, in properly treated cases, the "bridged over periods" should be utilized for the cleaning up of these depots, to bring about a complete cure. A fairly large number of private patients treated in this manner with equally satisfactory results are not included in this paper.

CONCLUSION

A "danger period" exists at the time of menstruation when gonorrheal salpingitis attacks are likely to occur or re-occur. Thirty thousand international units of follicular hormones, divided into 3 doses and given intramuscularly at three-day intervals with the onset of menstruation are recommended for bridging over this "danger period." Injection of 10,000 international units of follicular hormones at frequent or daily intervals is suggested in the treatment of acute gonorrheal salpingitis.

Very satisfactory results were obtained with this treatment, in 74 cases of chronic salpingitis and 91 cases of acute salpingitis over a period of thirty months.

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950 PARK AVENUE

ORAL PREGNENINOLONE IN THE TREATMENT OF SPONTANEOUS ABORTION

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THE purpose of this communication is to present the results of the treatment of a series of 50 consecutive cases of threatened and habitual abortion treated with oral pregneninelone.

All patients enrolled for obstetric care were given a supply of 5 mg. tablets of pranone* to have on hand. Those patients presenting a history of habitual abortion were instructed to take 10 mg. twice weekly until quickening occurred. In special cases, where a history of miscarriage in the later months of pregnancy was obtained, therapy was continued for a longer period. These patients were advised to record on a calendar the days that menstruation would occur if they were not pregnant. At this time their activity was restricted, and 10 mg. were given daily.

Patients with threatened abortion received a minimum of 10 mg. twice daily until all symptoms subsided, and then continued to take 10 mg. twice weekly for several months. Bed rest and occasionally barbiturates were the only other therapeutic measures. Morphine and its derivatives were not used because of the danger of stimulating uterine contractions.¹

RESULTS (TABLES I AND II)

A total number of 50 patients were treated with oral pregneninelone. Of these, 39 were patients who threatened to abort during the present pregnancy and gave no history of previous spontaneous abortion. The remaining 11 patients gave a history of previous spontaneous abortion. There were a total of 8 failures. Seven of these failures occurred in the group of threatened abortions. Although 6 of the 11 habitual abortion patients threatened to lose the existing pregnancy, there was only one failure in this group. These results compare favorably with, and closely approximate, those obtained in similar groups of patients treated with progesterone.¹⁻³

DISCUSSION

The value of the corpus luteum hormone, progesterone, in the treatment of spontaneous abortion has been demonstrated by numerous investigators. The experience of no less an authority on abortion than

*Pranone (anhydro-hydroxy-progesterone) supplied by the Schering Corporation.

Taussig⁴ has been, as he describes, "most satisfactory." He further states that, "in view of the small number of therapeutic measures available, this one should be employed in every case of habitual abortion."

TABLE I

CASE	NAME	AGE	GRAV.	PARA	THREAT- ENED	HABIT- UAL	DURA- TION OF GESTA- TION	RESULT
1	F. B.	28	iii	i	X	O	3 mo.	Normal baby at term
2	L. B.	27	iii	i	X	O	3 mo.	Normal baby at term
3	G. B.	30	i	0	X	O	4 mo.	Normal baby at term
4	H. C.	25	i	0	X	O	3 mo.	Failure
5	L. D.	20	iii	ii	X	O	6½ mo.	Normal baby at term
6	M. D.	32	ii	i	X	O	6½ mo.	Normal baby at term
7	R. D.	25	i	0	X	O	3 mo.	Normal baby at term
8	A. D.	22	iv	i	O	X	—	Normal baby at term
9	H. E.	26	i	0	X	O	5½ mo.	Normal baby at term
10	S. E.	22	i	0	X	O	2 mo.	Failure
11	J. F.	?	i	0	X	O	4 wk.	Failure
12	F. F.	26	i	0	X	O	2 mo.	Normal baby at term
13	H. F.	26	iii	0	O	X	—	Normal baby at term
14	M. F.	28	i	0	X	O	2 mo.	Normal baby at term
15	R. G.	24	i	0	X	O	4 wk.	Normal baby at term
16	S. G.	26	ii	0	O	X	—	Normal baby at term
17	S. G.	35	iii	0	O	X	—	Normal baby at term
18	B. H.	34	i	0	X	O	6 wk.	Normal baby at term
19	E. H.	20	i	0	X	O	2 mo.	Normal baby at term
20	H. H.	30	ii	i	X	O	2½ mo.	Failure
21	L. H.	29	iii	i	X	O	6 wk.	Normal baby at term
22	B. H.	24	iv	i	X	X	4 wk.	Normal baby at term
23	H. H.	35	iii	0	X	X	3 mo.	Failure
24	S. I.	34	ii	i	X	O	6½ mo.	Normal baby at term
25	J. K.	30	i	0	X	O	6 wk.	Normal baby at term
26	H. K.	24	i	0	X	O	3 mo.	Normal baby at term
27	S. M.	26	ii	0	O	X	—	Normal baby at term
28	A. R.	27	ii	0	X	X	3 mo.	Normal baby at term
29	H. R.	28	ii	i	X	O	3½ mo.	Normal baby at term
30	S. R.	32	i	0	X	O	2½ mo.	Normal baby at term
31	J. T.	32	ii	0	X	X	3 mo.	Normal baby at term
32	M. S.	25	iii	i	X	O	5 mo.	Normal baby at term
33	R. S.	25	i	0	X	O	3 mo.	Normal baby at term
34	B. S.	37	ii	i	X	O	3½ mo.	Normal baby at term
35	L. S.	25	ii	0	X	O	3½ mo.	Normal baby at term
36	W. W.	24	i	0	X	O	6 wk.	Normal baby at term
37	S. Z.	27	ii	i	X	O	6 wk.	Normal baby at term
38	T. F.	30	ii	0	X	X	6 wk. & 3 mo.	Normal baby at term
39	F. W.	32	ii	0	X	O	2½ mo.	Normal baby at term
40	H. S.	31	ii	0	X	O	6 wk.	Failure
41	R. F.	30	i	0	X	O	7 mo.	Normal baby at term
42	A. H.	33	i	0	X	O	2½ mo.	Normal baby at term
43	C. S.	20	i	0	X	O	6 wk.	Failure
44	R. L.	27	ii	0	X	O	6 wk.	Normal baby at term
45	R. E.	23	i	0	X	O	3 mo.	Failure
46	B. P.	31	i	0	X	O	6 wk.	Had myomectomy done at 4½ mo. Normal twins at term
47	J. W.	20	i	0	X	O	3 mo.	Normal baby at term
48	S. R.	21	i	0	X	O	3 mo.	Success. Undelivered as yet
49	G. F.	21	i	0	X	O	6 wk.	Success. Undelivered as yet
50	H. S.	28	iv	i	X	X	4 wk.	Success. Undelivered as yet

TABLE II

	NO. CASES	SUCCESS	FAILURE	PER CENT SUCCESS
Threatened abortion	39	32	7	82
Habitual abortion	11	10	1	91
6 of these patients threatened to abort during present pregnancy				
Total	50	42	8	84

The most recent and conclusive evidence in support of the logic of this form of therapy has been supplied by Browne, Henry, and Venning.⁵ They demonstrated that patients with threatening and habitual abortion show low urinary pregnanediol excretions.

The numerous advantages of oral therapy are easily recognized. It is a fact that there is a greater tendency for spontaneous abortion to occur at the expected menstrual time during the first few months of pregnancy. Physiologic investigations reveal that although, as a rule, ovulation ceases during pregnancy, the menstrual wave, as manifested by slightly increased body metabolism and increased nervous irritability, may persist for several months after conception in certain individuals.⁴ It is at this time that corpus luteum hormone therapy should be emphasized because of its inhibitory action on uterine motility. It is important for those patients, giving a history of habitual abortion, to remain inactive and avoid traveling to the doctor's office for injection at this time. The convenience to the patient and doctor of having tablets available at home is noteworthy. All patients under the care of an obstetrician could be supplied with tablets of pregnenolone, so that in case any signs of threatened abortion appeared therapy could be started without delay. Patients who insist on taking long automobile, train, plane, or boat trips against the advice of their obstetrician can prophylactically take this material. The cost involved is considerably less than progesterone in oil and within the means of the average patient. In considering the dosage of oral pregnenolone to be used, the fact that it is approximately one-sixth as potent as progesterone must be taken into consideration. Furthermore, it is probable that progesterone in oil has a more immediate effect than orally administered pregnenolone. At the present time we are investigating the effect of oral pregnenolone on human uterine motility and urinary pregnanediol excretions. Hamblen⁸ obtained no significant alterations in the urinary titers of sodium pregnanediol glucuronide and of androgens using this form of therapy. Cohen and Stein⁷ believe that caution should be exercised when administering pregnenolone therapy in the human being. This attitude is based upon their animal toxicity experiments in which they demonstrated tubular necrosis in the kidneys and cloudy swelling and hyperemia in the livers of rats. They also report mild undesirable effects, such as nausea, vomiting, abdominal pain, weakness and dizziness, and headaches in 31 per cent of their clinically treated patients, although no serious reactions or evidence of liver or kidney injury was observed. This evidence of toxicity has not been confirmed by other investigators.

of the gonadotropic activity of the hypophysis which results in suppression of ovulation and estrogen formation; (b) inactivation of the estrogens (or nullification of their biologic effects); and (c) inhibition of the proliferative capacity of the endometrium. Keeping these facts in mind, it is not difficult to explain the control of menorrhagia by massive doses of testosterone. The hypophysis is inhibited so that no gonadotropic hormone is secreted, estrogen production by the ovary is suppressed and, as a result of the rapidly developing deficiency in estrogens, and possibly also because of a direct inhibitory action of testosterone on the uterus, the normal proliferative changes are halted and involutional changes set in. Amenorrhea of variable duration ensues. When the testosterone propionate is stopped, its effects wear off gradually. The pituitary then resumes the secretion of gonadotropic hormones. The ovary responds with ovulation and estrogen and progesterone formation. The endometrium reacts to stimulation by estrogens and progesterone, creating a normal proliferative and secretory pattern which is ultimately shed, resulting in a normal amount of menstrual bleeding.

But how is one to account for the good therapeutic results obtained with small doses which do not suppress menstruation and do not produce the regressive changes in the endometrium? We must assume that, when administered in small doses, testosterone propionate produces a qualitatively similar, though less profound, effect. It is not difficult to conceive that testosterone may only partially inhibit, modify, or "mute" the factors which are involved in the causation of bleeding, and thus establish a normal bleeding cycle without completely suppressing estrogen formation or producing the marked involutional changes in the endometrium. It is true that in a number of our successfully treated patients a period of amenorrhea was first induced, and we cannot deny the possibility that the profound inhibitory effect of testosterone upon the pituitary, ovary, and endometrium may have been the cause for the subsequent establishment of the normal cycle. On the other hand, it should be pointed out that, in a number of cases, the same therapeutic effect was achieved with small doses, without inducing any of the demonstrable inhibitory effects. In any event, the conclusion seems warranted, in the light of our studies, that following the administration of testosterone, a readjustment occurs in the steroid sex hormone organization, which results in the establishment of a normal pituitary-ovarian-uterine relationship. And, as a result of this new order, normal cyclic uterine bleeding occurs. Recently, it has been suggested that testosterone propionate exerts its therapeutic effect through a two-fold action on the uterine musculature, causing "inhibition of the intermittent uterine contractions and a direct stimulative action upon the myometrial elements."^{71, 71} The basis for the "stimulative action" on the myometrium is the uterine hypertrophy induced in rats with testosterone propionate by Korenchevsky³⁹ and his co-workers. Unfortunately, androgens do not induce the same effects in women as they do in rats. Whereas, in rats, testosterone propionate has a stimulating (gynecomimetic) effect on the genital tract, it has an antigynecogenic action in cyclical women.

In order to understand the *modus operandi* of testosterone propionate, it is essential that we define, as clearly as possible, the factors that are involved in uterine bleeding, whether normal or abnormal. We can refer but briefly here to the established facts and generally accepted views. For comprehensive accounts of the experimental studies and theories relating to menstruation, the reader is referred to the reviews of Allen,³ Corner,¹¹ Bartelmez,⁴ Markee,⁴¹ Engle,¹⁸ and Ehrenfest.¹⁶ It is the consensus among workers in the field that uterine bleeding occurs whenever there is a withdrawal of estrogens or progesterone. The studies of Bartelmez,^{4, 5} Markee,⁴¹⁻⁴⁴ Daron¹⁴ and others have shown that the blood vessels of the endometrium are under control of the ovarian hormones. During the latter half of the cycle, the "spiral arteries" undergo rapid growth and become more strikingly coiled.¹⁴ After withdrawal of the growth stimulus a series of vascular changes occur which culminate in endometrial desquamation and menstrual bleeding. In spite of these ingenious and elaborate studies, we have very little information about the aspect of menstruation which is of paramount importance to the clinician, viz., *the factors that control the amount and duration of the bleeding.*

Our studies, as well as those of others, have shown that excessive bleeding may occur from an endometrium showing normal proliferation, a typical secretory pattern or hyperplasia. The abnormal bleeding, therefore, cannot be attributed to, or correlated with, any specific deviation from the normal endometrial pattern. Evidence is accumulating which seems to indicate that the importance of the endometrium, *per se*, has been overstressed in regard to abnormal bleeding and that the role of the endometrium may be purely a passive one. However, it is worthy of note that in all of the cases of abnormal bleeding, regardless of the type of endometrial pattern found, the endometria all indicate the presence of one factor common to all,* a factor which is apparently indispensable for uterine bleeding, whether normal or abnormal, viz., estrogen stimulation. And although the experimental studies in monkeys and human beings indicate that *withdrawal* of gynecogens initiates bleeding, it has also been our experience that, in women, bleeding may begin *during the course of estrogen administration*, providing the estrogen stimulation is sufficiently intense and maintained for an adequate length of time. Furthermore, we have reason to believe that bleeding may be prolonged by continued estrogen stimulation. Thus in patients implanted with estradiol crystals (in whom estrogen stimulation was maintained for many months), we have found evidence of active endometrial proliferation or hyperplasia even after a fourteen-day period of profuse bleeding.

It has been shown that if testosterone propionate is given in sufficient doses to women it can completely nullify the action of the estrogens and the other hormonal factors that are responsible for the initiation and continuation of bleeding, leading to suppression of menstruation and hypoplasia or atrophy of the endometrium. There is reason to believe that this effect is achieved through a combination of 3 actions, viz., (a) inhibition

*The exceptions to this are the comparatively uncommon instances of bleeding from an atrophic endometrium ("senile endometritis").

7. The use of testosterone propionate is recommended in the treatment of menorrhagia or menometrorrhagia of "functional" origin, or if associated with small intramural myomas. The results from testosterone propionate are likely to be unsatisfactory if the abnormal bleeding is associated with submucous myomas.

8. The one case of menorrhagia associated with adenomyosis of the uterus was controlled while under treatment, but experienced a complete recurrence of the excessive bleeding after the testosterone propionate was discontinued.

9. The signs and symptoms of testosterone propionate overdosage are described in detail.

10. The importance of studying the cytologic changes in the vaginal smears as a method of regulating the dosage is stressed.

11. A preliminary report on the use of methyl testosterone, ethinyl testosterone, and androgen implantation is presented.

12. A theory is formulated regarding (a) the modus operandi of testosterone propionate in controlling abnormal uterine bleeding and (b) the physiologic role of androgens in the normal steroid sex hormone balance of the human female.

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Physiologic Implications of Androgen Therapy.—The question naturally arises as to whether we are to consider the action of testosterone in the control of abnormal bleeding as a curious therapeutic phenomenon or as a form of physiologic substitution therapy, correcting a qualitative or quantitative androgen inadequacy. If we assume the latter, then, by implication, we automatically assign an essential role to androgens in the hormonal regulation of normal menstruation. Thus Koch and his co-workers^{23, 37} have shown that normal adult women excrete significant amounts of androgens (an average of 26 international units of androgens per day, as compared with an average of 40 units per day by males), whereas, before puberty the androgen excretion by girls is extremely small (from 1.8 to 2 international units per liter). It has also been shown that androgens excreted by women are chemically identical with those excreted by males.^{9, 75}

As to the function androgens may perform in the complex steroid sex hormone system of women, one must look to the biologic properties displayed by testosterone when it is administered to the cyclical human female. Our studies appear to indicate that, depending upon the dose administered, testosterone propionate tends either to modify or nullify the action of the gynecogenic hormones. And, on the basis of these observations, it is concluded that the endogenous androgens of the human female perform a function which is analogous to the action of exogenous androgens (testosterone propionate). The androgens and gynecogens are thus pictured as being normally in a state of dynamic balance. If the equilibrium is upset in favor of the gynecogens, the resulting imbalance would give rise to dysmenorrhea, menorrhagia, or premenstrual tension; if in favor of the androgens, to oligomenorrhea, amenorrhea, and hirsuties.

SUMMARY AND CONCLUSIONS

1. The results of the treatment of a group of 61 patients with menometrorrhagia with testosterone propionate are presented.
2. The series consists of 45 cases of functional bleeding, 15 cases of menometrorrhagia associated with uterine fibroids, and one case of adenomyosis of the uterus.
3. The effects of different doses of testosterone propionate upon menstruation, the endometrium and vaginal mucous membrane are described.
4. Good primary therapeutic results were obtained in 97.7 per cent of the cases of functional bleeding. Apparent cures (follow-up varying from three to thirty-two months) were obtained in 66.6 per cent; moderate improvement in 26.6 per cent; and failure in 6.8 per cent of the cases.
5. The results in the patients with uterine fibroids were not satisfactory. Although the primary results were good in 87 per cent, symptoms recurred after discontinuation of treatment in 60 per cent of the cases.
6. A preliminary report is made of the results obtained with implants of crystals and pellets of testosterone and testosterone propionate. The therapeutic results were unsatisfactory.

Clinicians began to apply this new mode of therapy to the treatment of the menopausal syndrome. P. M. Bishop³ found that the implantation of 14 mg. of estrone in the abdominal wall in a menopausal woman caused a marked decrease in the number of hot flushes within a period of one week; an effect maintained for approximately a month. The calculated daily absorption was 0.5 mg. or 5000 I.U.

Salmon, Water, and Geist⁴ described a technique of implantation in the gluteal region, and noted complete relief with substitution therapy of 4 to 7 mg. of crystalline estradiol benzoate. They concluded that 25 to 50 mg. should maintain a patient symptom free for many months and suggested that it be given prophylactically to patients following x-ray or surgical castration. MacBryde and others⁵ implanted 100 mg. of stilbestrol pellets in the lumbar region and were able to show endometrial proliferation in seven days.

Bennet, Biskind, and Mark⁶ reported a series of 21 menopausal patients who received compressed tablets of theelin. These pellets, 3 to 10 in number, weighing 5 to 16 mg., were loaded in a hollow 12-gauge needle and implanted by pressure with a stylet. Biopsies of the vaginal mucosa showed increased proliferation two weeks after treatment. All patients improved under treatment. Symptoms returned gradually and were relieved by second implantation. They noted no infection, inflammation, or abnormal uterine bleeding.

During the past year we have studied the effects of implantation of a single pellet of crystalline estrogens 45 to 65 mg. in weight, in a series of 28 cases. The technique employed was simple and is briefly described as follows: The site chosen for implantation was the region of the groin just above Poupart's ligament. Under $\frac{1}{2}$ per cent novocaine anesthesia, a small incision was made in the skin to allow the introduction of a small curved hemostatic forceps. A channel was made in the subcutaneous tissue and the hemostat withdrawn. The pellet was then introduced a few centimeters laterally to the line of the incised wound. The edges of the incision were then strapped together with sterile adhesive. No sutures were ever used. The patients did not complain of any adverse symptoms and the area healed by primary union within forty-eight hours. The procedure was simple and took but a few seconds longer than an intramuscular injection.

The cases chosen for this study were for the most part those with well-defined symptoms associated with the menopause. These, in turn, were subdivided into the following groups: namely, surgical and irradiation castration, and spontaneous menopause. The common symptoms of menopause, such as hot flushes, sweats, headaches, joint pains, nervousness, irritability, pruritus vulvae, and dyspareunia, were noted at the time of implantation. Vaginal smears, and in some instances, endometrial biopsies were taken during the period of observation. It was found that a week or ten days elapsed in most of the cases before any relief was noted by the patient. In no instance did any abnormal bleeding occur. No evidence of infection, inflammation, or foreign body reaction was observed.

A group of patients with primary amenorrhea were treated by implantation with estrogen pellets. The effect upon development of the secondary sex characteristics and growth in the size of the uterus were noted. It was found that in patients with complete lack of breast de-

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A CLINICAL STUDY OF ESTROGENIC THERAPY WITH PELLET IMPLANTATION

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THE value of estrogenic substitution therapy in the treatment of menopausal disorders is now well established. Heretofore, this has been accomplished by means of intramuscular injection, oral administration, and local application. In 1937, Deanesly and Parkes¹ studied a new method of administration of the hormone. They implanted subcutaneously highly compressed tablets of crystalline estrone in laboratory animals. They believed that by this method a continuous supply of the hormone could be released in the body, thus simulating the normal physiologic mechanism. They observed that the prolonged action was associated with increased effectiveness of the hormone per unit weight which was perhaps explained by more complete utilization (decreased waste). A year later the same authors² in another series of animal experiments studied the absorption rate of the implanted tablets and determined the quantity of hormone used per month by reweighing the implanted tablets at the termination of the experiment. The effects of this long-continued action were in most respects similar to those described by other authors as resulting from the repeated injections of estrogens and the resulting inhibition of formation of the gonadotropic and growth-promoting hormones of the anterior pituitary. As a result of these animal experiments, they suggested that the method would be useful in the treatment of conditions requiring a long-continued and uninterrupted estrogenic effect.

F. M., aged 28 years, had a panhysterectomy in 1939. Hot flushes occurred 15 to 30 times daily. Psychoneurosis. She was confined in Bellevue Psychopathic Hospital for two weeks. *Previous therapy*: Estrone 10,000 I.U. three times a week. Not satisfactory. *Implant*: April 6, 1940, 52 mg. estrogen.

Result.—One week after implant the flushes were absent. There was relief of all symptoms until Sept. 15, 1940. Return of libido and emotional stability. Gain in weight. Reimplantation on Oct. 5, 1940, of 50 mg. estrogen. On Dec. 14, 1940, she felt and looked well. There have been no flushes or emotional upset.

A. C., aged 53 years, had a hysterectomy in 1936. Hot flushes occurred 8 to 10 times daily. She had pruritus vulvae, nervousness, insomnia, and crying spells. *Previous therapy*: Estrone 10,000 I.U. twice a week for one year. Relief of symptoms. Recurrence after injections were stopped. *Implant*: Aug. 29, 1940, 56 mg. estrogen. *Smears*: Aug. 29, 1940, typical castration smear; Sept. 26, 1940, good estrogenic function.

Result.—Sept. 26, 1940, no flushes, itching, or burning. More energy. Still under observation.

M. B., aged 39 years, had irradiation in 1939 for menorrhagia. Hot flushes occurred 20 to 30 times daily. Severe headaches. *Previous therapy*: Estrone 30,000 to 40,000 I. U. twice a week for six months. No relief. *Implant*: April 6, 1940, 55 mg. estrogen. *Smears*: April 6, 1940, typical castration cells; May 5, 1940, moderate function. *Biopsy*: May 5, 1940, complete atrophy of endometrium.

Result.—May 5, 1940, flushes now 10 daily. Patient did not return for further observation or therapy. Partial improvement, no effect upon endometrium.

M. C., aged 42 years, had postradiation in 1937 for fibromyoma. Severe hot flushes occurred 5 to 10 times daily. Nervousness, irritability, insomnia, dyspareunia were present. *Previous therapy*: Estrone 10,000 I.U. once or twice a week for two years. Moderate but transient relief. *Implant*: June 15, 1940, 50 mg. of estrogen. *Smears*: June 17, 1940, decreased estrogenic function; July 8, 1940, excellent estrogenic function; Sept. 23, 1940, decreased function.

Result.—Complete relief of all symptoms for three months. After September 15, she noticed recurrence of flushes. Reimplanted Sept. 28, 1940, 57 mg. of estrogen. Complete relief of all symptoms when last seen, Dec. 23, 1940.

GROUP II. SPONTANEOUS MENOPAUSE

A. N., aged 40 years, had a spontaneous menopause 1 year previously. Hot flushes occurred from 15 to 20 times daily. She was nervous and had lost weight (18 pounds). *Previous therapy*: 10,000 to 20,000 I.U. estrone per week sporadically with moderate relief. Flushes occurred 5 or 6 times a day. *Implant*: April 18, 1940, 50 mg. of estrogen. *Smears*: April 1, 1940, typical castration smear; Sept. 12, 1940, good estrogenic function.

Result.—Complete relief two weeks following implantation. Duration, 5 months. Reimplantation on Sept. 26, 1940, of 58.5 mg. of estrogen following return of symptoms. Still under observation.

K. L., aged 50 years, had a spontaneous menopause complicated with thyrotoxicosis and hypertension. Blood pressure 230/110 (June 1, 1940). Vertigo, tinnitus, vomiting, hot flushes were present. *Previous therapy*: Thyroidectomy four months before. No estrogenic therapy. *Implant*: June 1, 1940, 57 mg. of estrogen. *Smears*: June 1, 1940, slight estrogenic function; July 2, 1940, excellent estrogenic function; Sept. 2, 1940, good estrogenic function; Sept. 20, 1940, decreased estrogenic function. Basal metabolic rate plus 22 per cent. Blood cholesterol 107 mg. per 100 c.c. of plasma (June 3, 1940).

Result.—Two weeks following implant, symptoms improved. No vertigo, vomiting, or tinnitus. Blood pressure 200/110, on Sept. 26, 1940. Return of symptoms five months later. Reimplantation of 59.5 mg. of estrogen Nov. 7, 1940. Has been able to do all housework and is symptom free up to present time, Dec. 23, 1940.

W. J., aged 48 years, had spontaneous menopause 3 years ago. Hot flushes 6 to 10 times daily. She was nervous, irritable, and had pruritus. *Previous therapy*:

velopment, a remarkable increase in size of both the nipple and mammary gland was observed in a comparatively short period of time, i.e., five to six weeks.

Several patients with secondary amenorrhea of long standing were treated with estrogen pellets, and the effect upon the menstrual cycle and the size of the uterus were noted. In this group, the patients did not experience any change in their symptoms unless the secondary amenorrhea was associated with signs of early menopause. The cases are briefly described as follows:

GROUP I. SURGICAL AND IRRADIATION MENOPAUSE

C. R., aged 32 years, had a panhysterectomy in 1939. She had hot flushes, 10 to 15 daily, severe headaches, nervous irritability, and loss of appetite. *Previous therapy*: estrone 20,000 I.U. every week for two months. There was moderate improvement. *Implant*: June 22, 1940, 56 mg. estrogen. *Smears*: June 22, typical castrate smear. September 14, good estrogenic function. October 19, fair estrogenic function.

Result.—All symptoms disappeared up to Oct. 19, 1940, at which time headaches returned. Complete relief four months.

M. K., aged 40 years, had a hysterectomy in 1938. She had hot flushes and severe itching and burning of vulva and vagina. *Previous therapy*: estrone 10,000 I.U., twice a week at intervals for one year with relief of flushes, but not of pruritus. Estrogenic ointment for six months with relief of burning and itching. *Implant*: Aug. 19, 1940, 63.5 mg. estrogen. *Smears*: Mar. 7, 1940, slight function; Sept. 26, 1940, good estrogenic function.

Result.—Relief of all symptoms to date, four months after implantation. No evidence of pruritus vulvae.

Y. S., aged 40 years, had a hysterectomy in 1937. Hot flushes occurred 6 to 8 times daily. Severe headaches. *Previous therapy*: Estrone 10,000 I.U. twice a week for one year. Moderate relief of flushes. *Implant*: Feb. 27, 1940, 60 mg. estrogen. *Smears*: Feb. 14, 1940, marked decrease estrogenic function; March 12, 1940, good estrogenic function.

Result.—Relief of all flushes. Persistence of headaches. Referred for allergy study after two months' observation.

E. Z., aged 43 years, had a hysterectomy in 1937. Hot flushes occurred 10 to 15 times daily. Severe pruritus vulvae. *Previous therapy*: Estrone 10,000 I.U. once or twice a week from June 29, 1940, to Sept. 7, 1940. Flushes reduced, 2 daily. Pruritus unaffected. *Implant*: Sept. 7, 1940, 53.5 mg. estrogen.

Result.—Complete relief of all symptoms two weeks after implant. Oct. 19, 1940, patient in excellent condition. No flushes or pruritus. Last observed on Dec. 21, 1940, condition excellent.

E. B., aged 40 years, had a bilateral oophorectomy in 1930. Pruritus vulvae. Flushes occurred 6 to 8 times daily. Examination, atrophic vaginitis. *Previous therapy*: Estrone 10,000 I.U. once or twice a week at intervals. Relief of flushes but not of pruritus. *Implant*: June 1, 1940, 64 mg. estrogen.

Result.—Sept. 21, 1940, no flushes. Itching disappeared. Mucous membrane healthy. Oct. 5, 1940, occasional itching and few flushes. Complete relief after four months' treatment.

F. G., aged 42 years, had a hysterectomy in 1930. Hot flushes occurred 10 to 15 times daily. Emotional disturbance. *Previous therapy*: Estrone 10,000 I.U. twice a week from Dec. 30, 1939, to May 1, 1940. Symptoms returned when treatment was stopped. *Implant*: May 1, 1940, 68.8 mg. estrogen. *Smears*: May 1, 1940, 10 per cent function; July 7, 1940, 90 per cent function.

Result.—Complete relief after five and one-half months after implantation. Re-implantation on Nov. 2, 1940, of 62.5 mg. of estrogen.

Result.—No flushes. General condition much improved for period of six months. Return of symptoms October, 1940. Reimplantation on October 10 of 57.5 mg. of estrogen. Still under observation. Symptom free to date, Dec. 24, 1940.

M. R., aged 35 years, had menopause precox. Her last menstrual period occurred in December, 1935. Hot flushes occurred 3 to 4 times daily. There were malaise and absence of libido. *Previous therapy*: Sporadic treatment with injections of estrone for two years. No effect on general condition. *Implant*: Aug. 15, 1940, 55 mg. of estrogen. *Smears*: August 15, typical castration cells; September 26, very good estrogenic function. *Biopsy*: Oct. 11, 1938, atrophic endometrium (Fig. 1). Oct. 3 and 17, 1940, proliferative endometrium (Fig. 2).

Result.—All symptoms were relieved three weeks after implantation. No flushes, return of libido. She was able to do all housework. Three months later, reappearance of symptoms, followed by reimplantation of 60 mg. of estrogen on Nov. 18, 1940. Still under observation.

A. G., aged 47 years, had decreased menstrual periods for two years. She also had severe hot flushes, twitching of eyelids, insomnia, and nervousness. *Previous therapy*: Estrone 10,000 I.U. twice a week. Moderate but transient relief. *Implant*: Aug. 19, 1940, 56.5 mg. of estrogen. *Smears*: October 7, fair estrogenic function.

Result.—Flushes completely disappeared one week after implant. She sleeps better, and is not so nervous. Still under observation four months after implantation.

E. C., aged 45 years, had had scant periods for two years. She also had headaches, hot flushes, 4 to 5 times daily, lack of libido, and was always tired. There had been no previous therapy. *Implant*: Aug. 31, 1940, 46 mg. of estrogen. *Smears*: August 31, poor estrogenic function; September 19, excellent estrogenic function; October 3, excellent estrogenic function.

Result.—Oct. 3, 1940, feels well. There are no flushes or headaches, and she has more energy. There is marked improvement clinically. Still under observation four months after implantation.

D. D., aged 31 years, had menopause precox. She had had irregular periods for one year, every two to three months with one-hour flow. There were severe headaches, hot flushes, and absence of libido. There had been no previous therapy. *Implant*: May 4, 1940, 45 mg. of estrogen. *Smears*: May 4, no estrogenic function; May 18, fair estrogenic function; September 21, decreased function. *Biopsy*: September 21, abortive secretory phase.

Result.—June 15, increased sense of well-being. No flushes or headaches were present. Relief of symptoms for five months.

R. T., aged 27 years, had menopause precox. Hot flushes occurred 20 times daily. She had had amenorrhea for three years. *Previous therapy*: Substitution therapy 10,000 I.U., three times a week, thyroid. *Implant*: Aug. 28, 1940, 38.5 mg. of estrogen. *Biopsy*: Feb. 17, 1940, extreme atrophy.

Result.—Flushes were slight, 2 to 4 times daily, one month after implant. Libido increased. There was relief of symptoms for three months. Flushes reappeared Nov. 23, 1940, but not as severe as before. Reimplantation of 47 mg. of estrogen on November 23.

L. D., aged 32 years, had pruritus vulvae, dyspareunia, atrophy of vulva, and leucoplakia of vulva. *Previous therapy*: Estrogenic ointment for one year at intervals. Moderate relief while under therapy. *Implant*: June 1, 1940, 46.5 mg. of estrogen. *Biopsy*: October 1, nonfunctioning endometrium. *Vaginal biopsy*: parakeratosis.

Result.—Complete relief of all symptoms for four months. Return of itching and soreness Oct. 1, 1940. Leucoplakia of buccal mucous membrane 1 cm. in area anterior to Stenson's duct noticed on Oct. 26, 1940. Itching was worse. Reimplantation of 53.5 mg. of estrogen on Dec. 7, 1940.

GROUP III. PRIMARY AND SECONDARY AMENORRHEA

B. P., aged 23 years, had primary amenorrhea, absence of breast development and pubic hair. There had been no previous therapy. *Implant*: Dec. 5, 1939, 75 mg. of estrogen. *Smears*: December 5, no function; Jan. 15, 1940, excellent function.

Estrone 10,000 I.U. once or twice a week, and for 2 years had relief from flushes. *Implant*: May 6, 1940, 52 mg. of estrogen. *Smears*: March 18, typical castration cells; June 23, excellent estrogenic function; September 5, good estrogenic function; October 1, return of castration cells.



Fig. 1.—Endometrial biopsy before therapy; nonfunctioning endometrium cystic glands. Dense stroma.



Fig. 2.—Seven weeks after implantation of 55 mg. of estronic pellet. Moderate proliferation of endometrial glands, showing effect of mild estrogenic activity.

Result.—Two weeks after implantation, complete absence of flushes. General feeling of well-being. Duration, four and one-half months. Reimplantation on Oct. 1, 1940, of 56 mg. of estrogen, with alleviation of symptoms one week later. Still under observation.

P. H., aged 53 years, had a spontaneous menopause since June, 1939. Hot flushes occurred 2 to 4 times daily. Nervousness, insomnia, and irritability were present. She had had no previous therapy. *Implant*: April 18, 1940, 50 mg. of estrogen. *Smears*: April 18, marked decrease of ovarian function; May 19, excellent estrogenic function; October 5, decreased function.

We observed no undesirable or toxic effect in our series of cases with the preparation of oral pregnenolone which we used, although in many patients large doses were given over a period of many months. Our experience in treating gynecologic disorders also indicates that this material is innocuous.

CONCLUSIONS

1. A series of 50 patients with threatened and habitual abortion were treated with oral pregnenolone (anhydro-hydroxy-progesterone), and there were only eight failures.

2. The results obtained with oral pregnenolone compare favorably with and closely approximate those obtained using progesterone in oil.

3. Oral pregnenolone, although not as potent milligram for milligram as progesterone, presents numerous advantages.

4. No undesirable or toxic effects as the result of the administration of this drug were noted.

5. Oral pregnenolone is of distinct value in the treatment of threatened and habitual abortion.

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PRELIMINARY REPORT ON THE TRANSPORTATION OF MATERIALS FOR GONOCOCCAL CULTURES*

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SOME months ago a study was undertaken for the purpose of evaluating certain measures of therapy in gonococcal infection in women. It was felt that cure must be based on negative cultures as well as smears. McLeod,¹ Carpenter,² Malcom³ and others have amply demonstrated the value of cultures in the diagnosis of infection and have pointed out the probable advantages in determination of cure. Most of the results reported, however, have dealt with but one or two cultures from each patient. In determination of cure of infection, it is of considerable importance to know whether repeated consecutive smears may be negative while cultures remain positive.

*This work has been done under a grant from the Albert B. Kuppenheimer Foundation, Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-in Hospital.

Result.—There was noticeable development of both breasts within eight weeks, slight growth of pubic hair, but no menstrual period occurred.

F. S., aged 20 years, had primary amenorrhea. Hypertrichosis. *Previous therapy:* X-ray stimulation of pituitary. Substitution therapy. Infantile uterus on examination. *Implant:* April 6, 1940, 50 mg. of estrogen; Aug. 21, 1940, 57 mg. of estrogen.

Result.—Uterus was slightly larger. There was spotting from September 14 to 17. First real period occurred on October 29 to November 4. Breasts are larger, and the patient feels well.

E. J., aged 30 years, had primary amenorrhea. Hot flushes occurred 6 to 8 times daily. She had dyspareunia, and no breast development. *Previous therapy:* Substitution therapy 10,000 I.U., three times a week. *Implant:* April 28, 1940, 48 mg. of estrogen.

Result.—There had been no flushes six months after pellet implantation. Dyspareunia improved. Patient felt much better with implantation than with injections. Reimplantation of 59 mg. of estrogen Oct. 17, 1940, following return of flushes. Breasts were noticeably larger within eight weeks after implantation, but became smaller four months later.

A. W., aged 29 years, had secondary amenorrhea. Last menstrual period occurred May, 1940. Periods were at prolonged intervals of 6 months. *Examination:* Hypoplasia of uterus. No previous therapy. *Implant:* Aug. 18, 1940, 58 mg. of estrogen. *Biopsy:* September 26 nonfunctioning endometrium.

Result.—Failure. Patient was referred for x-ray therapy to pituitary. (Stimulation.)

B. M., aged 32 years, had secondary amenorrhea. There had been amenorrhea for one year. No previous therapy. No menopausal symptoms. *Implant:* Feb. 24, 1940, 50 mg. of estrogen; Aug. 14, 1940, 51.5 mg. of estrogen. *Smears:* February 24, no function; March 30, excellent function; April 13, moderate function; June 8, fair function; September 12, moderate function. *Biopsies:* February 11, atrophy; March 23, active proliferation; April 6, atrophy; September 11, irregular proliferation; October 4, atrophy.

Result.—Spontaneous period occurred on September 12 for three days, otherwise no change in menses.

A. P., aged 25 years, had secondary amenorrhea for nine and one-half months. There had been loss of libido. *Previous therapy:* Thyroid, and estrone 10,000 I.U. three times a week. *Implant:* Sept. 7, 1940, 55 mg. of estrogen. *Smears:* September 7, fair estrogenic function; September 28, excellent estrogenic function. *Biopsies:* July 24, atrophy; August 28, mild proliferation.

Result.—There was a spontaneous menstrual period on October 18 for four days. She is still under observation. No effect on libido.

DISCUSSION

Group I. Surgical and Irradiation Menopause.—Of the 10 menopause castration cases, 8 patients were relieved of all symptoms one week to ten days following implantation. There was 1 failure in a post-radiation case. One patient was observed only a short period of time and no definite conclusion could be made in this instance. Of the 6 patients kept under observation for a sufficient length of time, it was found that the average symptom-free period was four months. One patient, following radiation therapy, was symptom free for a period of three months. These patients were in a much younger age group than those of the spontaneous menopause. Considering the average dose to be 50 mg. and the average symptom-free period one hundred and twenty days, it would appear clinically that the patients utilized approximately 4,100 I.U. of estrogen per day.

Group II. Spontaneous Menopause.—Twelve patients with spontaneous menopause were treated with pellets, averaging 50 mg. in weight. As in the castration cases, a latent period of one week to ten days elapsed before relief in symptoms was noted by the patients. No abnormal bleeding occurred at any time following the implantation. The duration of the symptom-free period, in those patients observed for a sufficient length of time, averaged five months. This was a longer period than existed in the castration group. Roughly, therefore, from clinical observation alone, we may assume that 50 mg. will last one hundred and fifty days, and the patient absorbs an average amount of 3,000 I.U. per day.

Recently, Corner⁷ determined the rate of secretion of estrogenic hormones by the ovaries of the *Macacus rhesus* monkey in an experimental study. He estimated the rate of secretion tentatively as equivalent to 200 I.U. estrone daily. He multiplied this figure by a factor of 15 to allow for the proportionate weight and calculated the rate of production of estrogenic hormone by the human female as equivalent to 3,000 I.U. of estrone daily. There is a striking similarity of the figures obtained by Corner in the production rate of estrone as compared with our clinical estimate of utilization of the hormone in a group of spontaneous menopause cases.

It is interesting to note that those patients who had previous courses of intramuscular injections were able to compare the two forms of therapy. They stated that although intramuscular injections relieved their flushes, intermittently, they did not have the same continuous feeling of well-being, or energy, as when under therapy by pellet implantation. When questioned as to the type of therapy they preferred, they unanimously chose pellet implantation.

It has been the clinical observation of many workers that small amounts of ovarian hormone injected daily give far better results than large amounts administered once or twice a week. This fact was recently brought out by Smith⁸ in an analysis of 77 cases of estrogen therapy of the climacteric. It has been his practice to give daily intramuscular injections of 2,000 to 5,000 I.U. of estrone for a period of two or three months in moderately severe cases.

It is a well-known fact that only 15 to 20 per cent of climacteric women require intensive substitution therapy. However, these patients will not submit to long-continued intramuscular injections either daily or every other day. In the usual course of events, as soon as the patient feels better after the first few weeks of therapy, she will become negligent, and the treatment then becomes quite sporadic. Obviously, a method which will afford a continuous flow of hormone over a long period of time, following a single treatment, has tremendous appeal to the patient.

Another clinical observation was made in the pruritus vulvae cases associated with menopause. Some of these patients had previously been treated with estrogenic ointment, both for atrophic and hypertrophic vulvitis. They found that when the ointment was discontinued, their symptoms returned rather promptly and they were much more comfortable for a longer period of time under pellet therapy, especially

in cases of atrophic vulvovaginitis, where long-continued therapy caused increased changes in growth and vascularity of the vaginal mucous membrane. Many patients who complained of frigidity and dyspareunia found that these symptoms were definitely relieved.

Group III. Primary and Secondary Amenorrhea.—In 2 cases of secondary amenorrhea, biopsies showed evidence of a moderate proliferation of the endometrium. Vaginal smears showed an increased amount of cornified epithelial cells. An increase was noted in the size of the uterus which had previously shown evidence of hypoplasia. Implantation had no effect whatsoever upon the menstrual cycle. This observation is, perhaps, consonant with the accepted theory of menstrual bleeding as a deprivation effect. In pellet implantation the effect is continuous, and there are no periods of withdrawal at which times bleeding might be expected.

Three patients with primary amenorrhea were treated with implantation of estrogen pellets, averaging 55 mg. in weight, in order to observe the effect of long-continued administration upon the size of the uterus and upon the development of the secondary sex characteristics. The effect upon breast development in these cases was rather striking. Within a period of five to eight weeks, a noticeable increase in the size of the mammary glands and of the nipple area occurred. Lack of breast development was a disturbing factor in the patient's psyche. This was relieved after development took place in a comparatively short period of time.

CONCLUSIONS

1. Estrogen therapy by implantation of 50 mg. pellets is a safe and effective mode of therapy in cases of menopause.

2. Long-continued administration by implantation is more economical to the patient.

3. Pellet implantation is a simple office procedure.

4. No untoward effects were observed in a series of 28 cases.

5. Therapy by pellet implantation for the menopausal syndrome has proved more effective than that obtained by intramuscular injection.

6. In patients with primary amenorrhea, complaining of lack of breast development, satisfactory results have been obtained with pellet implantation.

The pellets used in this study were composed of the finely powdered estrogenic compounds derived from pregnant mares' urine (estrone, equilin, equilenin, and estradiol). The material was compressed in a steel die punch tablet machine without addition of any inert diluent. Material was furnished through the courtesy of Dr. C. F. Longfellow of G. W. Carnrick Co., Newark, N. J.

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CLINICAL EXPERIMENTS WITH DIETHYLSTILBESTROL*

II. THE TREATMENT OF UTERINE BLEEDING

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THE estrin deprivation theory of menstruation, even though inadequate for the complete understanding of the problem, has been the basis for the treatment of excessive or prolonged uterine bleeding with estrogenic hormone. Such rationale presupposes that uterine bleeding, when present, is a manifestation of relative or absolute ovarian deficiency.

Wintz,¹⁰ as early as 1924, used estrogenic hormones clinically for the treatment of uterine bleeding. He found the method successful in many types of bleeding, including that associated with uterine fibromyomas and abortion. Numerous other reports dealing with the subject have appeared. Those giving special emphasis to the mechanism involved include papers by Goldstine and Fogelson¹ (1931), Siebke⁹ (1933), Runge⁸ (1934), Martius⁵ (1934), Hamblen^{2, 3} (1936, 1939), and Karnaky⁴ (1940).

I have used diethylstilbestrol in the treatment of uterine bleeding in 31 patients of ages ranging from 12 to 55 years. In a previous paper,⁷ I reported the production of artificial menstrual cycles with threshold doses of diethylstilbestrol in women in whom ovarian function was absent. Cyclical treatment was arranged for patients with cyclical uterine bleeding in a similar manner, viz., 1 mg. of diethylstilbestrol per day for seven days, then 5 mg. a day for seven days, followed by 0.3 mg. a day for ten days, or until bleeding recurred. The treatment was started on the third day of bleeding. In most instances bleeding that usually lasted from eight to ten days ceased promptly the first or second day after diethylstilbestrol was started.

If the theory that *relative* ovarian deficiency is an etiologic factor responsible for uterine bleeding is sound, it follows that instances might occur where bleeding would take place in the presence of a high estrin level. In such cases a routine plan of therapy might fail since the dose of 1 mg. of diethylstilbestrol per day might not be sufficient to raise the estrin level above the uterine threshold. When, as it occasionally did, the plan failed, larger doses, up to 15 mg. per day, were used at the outset. The criterion of sufficient dosage was the cessation of bleeding within two days after treatment. When the dose was insufficient there was actually an increase in the amount of bleeding. Subsequent lowering of the dosage to a maintenance level of 1 or 2 mg. a day usually led to an interval free of bleeding for as long as the patient continued to take the drug. Thus in practice it was found advisable to continue the daily administration of diethylstilbestrol for from two to three weeks or until bleeding recurred.

*This study was made possible by the Christine Breon Fund for Medical Research.

RESULTS

Thirty-one patients, ranging in age from 12 to 55 years, complained of uterine bleeding. Classified according to age these patients fell into three groups as follows: (1) menorrhagia of puberty, (2) functional menorrhagia in women of reproductive age, and (3) menopausal bleeding.

Group I.—One patient only, 12 years of age, comprises the first group of menorrhagia of puberty. One cycle of therapy was administered and bleeding ceased promptly the second day of treatment after thirty days of profuse bleeding. The patient has had three subsequent periods which required no further intervention.

Group II.—Ten patients, 21 to 35 years of age, comprise the second group in which the complaint was regularly occurring but profuse and/or prolonged menstrual flow. Seven of these have required but one cycle of therapy. The other three have required 2, 3, and 5 cycles of therapy, respectively.

Group III.—Twenty patients comprise the menopausal bleeding group which consists of individuals whose ages range from 38 to 48 years. In addition to hot flashes, 5 of this group had uterine fibromyomas, 2 had cystic glandular hyperplasia of the endometrium, and in 2 the bleeding had been induced by uncontrolled estrogen therapy. There was no history or other evidence upon examination and endometrial biopsy suggestive of cervical or endometrial malignancy in these patients. Ten of the patients in this group have required but one cycle of stilbestrol therapy. Five have required 2 cycles, 3 have required 3 cycles, and 2 have required 5 cycles of therapy. An additional patient 55 years of age was included in this group because of special interest. Profuse uterine bleeding occurred spontaneously in this individual two months following the implantation of pellets of crystalline α -estradiol.* After twenty days of bleeding she stopped completely the second day of diethylstilbestrol therapy. (The selection of patients for pellet implantation is regularly restricted to patients in whom all pelvic organs have been removed to obviate the occurrence of uterine bleeding. However, in the case cited, the supravaginal hysterectomy performed had apparently failed in the complete removal of reactive endometrium.)

The patients have been so individualized as to their treatment that a table giving data is not practical. Fifty-seven cycles of therapy have been given in which the total dose of diethylstilbestrol ranged from 5 to 94 mg. with an average of 40 mg. per cycle.

Evidence that uterine bleeding actually is a manifestation of ovarian deficiency was demonstrated in most of the patients treated by an abnormally high vaginal pH (5.0 to 7.0) during an interval free from bleeding. This finding was usually associated with a thin, inelastic and atrophic vaginal membrane in the menopausal patients. The lowering of the pH to 4.0 to 4.5 and remission of bleeding followed the administration of diethylstilbestrol. Menopausal women are prone to have menorrhagia associated with other symptoms of failing ovarian function. One of the patients in this series with the diagnosis of cystic glandular hyperplasia of the endometrium has been studied from the standpoint of estrogen excretion in a report dealing with the occurrence of free estrogen associated with uterine bleeding (Palmer⁶). This disease, often referred to clinically as "hyperestrinism," was not associated with excessive urinary estrogen excretion. Urinary hormone assays by numerous observers adequately demonstrate that normal menstruation occurs when the urinary excretion of estrogen is at its lowest level. Such observations are of the kind that give significance to the estrin withdrawal theory of menstruation and support the view that uterine bleeding is a manifestation of a relative "hypo-estrinism" rather than "hyperestrinism."

There was no consistency in the duration of the latent interval between the cessation of diethylstilbestrol treatment and the onset of the next uterine bleeding. Sometimes bleeding occurred before the cessation of a course of treatment and in other instances there was no recurrence of bleeding for as long as six or seven weeks. The marked variability in the length of the latent interval between the cessation of stil-

* α -Estradiol was supplied by the Ciba Company.

bestrol therapy and the occurrence of uterine bleeding, as well as the occurrence of bleeding in some instances during therapy, can only be interpreted as reflections of falls in the degree of estrogenic stimulation experienced by the patient. As in the monkey (Zuckerman¹¹), it follows that periodical changes occur within the patient of a kind that decreases the effectivity of diethylstilbestrol. When the bleeding did occur and if it was profuse in nature, another cycle of diethylstilbestrol therapy was started. Occasionally the bleeding which followed one cycle of treatment was normal as to amount and duration of flow so that further treatment was unnecessary. In all instances but one the occurrence of bleeding following the first cycle of treatment was less severe than previously.

The experimental data on human beings are not intended to show a superiority of diethylstilbestrol over any of the naturally occurring and other synthetic estrogens. The availability of large amounts of this estrogen, however, makes it possible to demonstrate the efficacy of estrogens in inhibiting uterine bleeding in every instance observed, in a short period of time, with subsequent bleeding of less severity. It appears that unusually large doses as used by Karnaky⁴ are unnecessary and in view of the reported toxicity of the drug such large doses should be avoided. Hamblen² and Karnaky⁴ have reported the same successful results with the use of estradiol benzoate injected intramuscularly. Daily oral therapy, however, for the purpose of maintaining a level of estrogen without the inconvenience and discomfort of intramuscular injections is probably desirable.

Recently ethinyl estradiol* for oral use has been available and already this newest of estrogens shows promise of accomplishing the same desirable effects in the controlling of uterine bleeding. At present, it appears that ethinyl estradiol is effective in smaller doses than are required of diethylstilbestrol.

Nausea and occasional vomiting have occurred in 11 (35 per cent) of the patients under treatment. Details of toxicity studies and disturbed liver function are to be reported elsewhere. Suffice it to say that a reduction of the liver's ability to synthesize hippuric acid (Quick, 1939) has been observed in several patients during treatment with diethylstilbestrol. Recovery of this function appears to be complete in instances where the test has been carried out two weeks after cessation of treatment. Diminished liver function has not been apparent in individuals who have received 1 gram of aminoacetic acid† per day simultaneously with the administration of diethylstilbestrol. The occurrence of nausea and vomiting has not been so troublesome since this material has been used with diethylstilbestrol.

SUMMARY

1. A view is taken that uterine bleeding is symptomatic evidence of that critical state when the uterine threshold to estrogen is above estrin level. Thus normal menstruation or abnormal uterine bleeding is considered to be primarily a manifestation of a relative or absolute ovarian deficiency. This view is supported by the finding of abnormally high

*Ethinyl estradiol was supplied by the Schering Corporation.

†Aminoacetic acid was supplied by the Dow Chemical Company.

vaginal pH values before treatment. Remission of bleeding coincidently with the lowering of the vaginal pH occurred with diethylstilbestrol therapy.

2. Thirty-one patients with abnormal uterine bleeding, ranging in age from 12 to 55 years, were treated with diethylstilbestrol. For the present, the plan adopted for such treatment in young women with functional menorrhagia is 1 mg. of diethylstilbestrol a day for seven days, 5 mg. a day for seven days followed by a decrease in dosage to 0.3 mg. per day for ten days or until bleeding recurs. Such a cycle of therapy is begun on the second or third day of a phase of uterine bleeding or as soon as the patient presents herself if she is bleeding when first seen. For the older women with menopausal bleeding, treatment is begun with a larger dose, 5 to 15 mg. a day until the bleeding ceases. A maintenance dose of 1 or 2 mg. per day is continued for three weeks or until bleeding recurs. Cessation of bleeding is the criterion of sufficient diethylstilbestrol dosage.

3. The existence of a fluctuating uterine threshold to diethylstilbestrol in women with uterine bleeding has been demonstrated. Theoretical as it may be and possibly a manifestation of rhythmical activity on the part of the adrenal or pituitary or both, this factor must nevertheless be taken into account when estrogens are administered to menstruating women. Although this form of therapy may only be temporary in some instances, it has its place as a means of stopping bleeding quickly in cases where other methods of treatment short of hysterectomy have failed. It may be made use of in controlling uterine bleeding preoperatively in cases of fibromyomata uteri.

The diethylstilbestrol used in this investigation was supplied by the Eli Lilly and E. R. Squibb Companies.

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The investigations of Bayer lead him to agree with others that there is a preponderance of male fetuses in every month of pregnancy except the eighth. At full term there are 105.6 boys to every 100 girls. However, at the beginning of pregnancy and in the early months, the ratio is 124.2 males to 100 females. Furthermore, there is an increased death rate among the male fetuses in every month except the eighth and including labor. This ratio of fetal deaths is 110.3 males to 100 females. Hence, there is a distinctly higher resistance of female fetuses during intrauterine development.

PSYCHOGENIC AND SOMATOGENIC FACTORS IN THE FLUSHES OF THE SURGICAL MENOPAUSE*

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IN NOVEMBER, 1939, observations on certain of the peripheral vascular effects of estrogen in menopausal women were commenced in Greenpoint Hospital. Since it was hoped to obtain objective information on the dermovasculature action of the hormone in postmenopausal patients, uncomplicated by psychic factors, it was decided to employ only those who presented themselves at the gynecologic out-patient clinic with a primary complaint of intense and frequent menopausal flushes, and in whom no complicating medical or other predisposing factor was discernible on routine examination.

In accordance with current concepts,³ it was believed at the outset that the most common symptom of the menopause syndrome after surgical removal of the ovaries, or after x-ray sterilization, is vasomotor instability, usually with the absence of well-marked psychic signs. It was planned, therefore, to use such patients for the most part. By so doing, it was thought that more objective studies could be made. This was particularly desired, since it has been observed recently⁴ that whereas vascular disturbances in the menopausal and postmenopausal period respond to estrogen therapy, the neurotic and psychotic aspects of the syndrome are unaffected by the hormone. Consequently, it was a matter of some surprise to observe that in not a small proportion of this group of patients (10 out of 13) in whom artificial menopause had been induced, it was possible to relate relief from the menopausal flushes to specific readjustment of some psychogenic, medical, or social problem. The present report recounts these experiences, resulting from careful study of the patients for periods lasting up to twelve months. It may be well to emphasize that the presence of such factors seldom was revealed in early interviews, but only later when the patients became more talkative and the conditions of the vascularity experiments became less strange.

OBSERVATIONS

Twenty-four patients comprise the group employed in this study. Of these, 6 (3 in natural menopause and 3 in surgical menopause) were eliminated from study

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We are indebted to Dr. Thurston Scott Welton, Chief of the Service on which these studies were made, for the privileges extended to us, and for interest in the progress of the work.

without relief, because they suffered from a variety of conditions that rendered them unsuited to, or uncooperative for, the primary object of our vascular study. These included essential hypertension, proliferative hypertrophic arthritis, acrocyanosis with rachialgia and hypothermia, paranoid conditions and extreme melancholia with undernutrition. Of the remainder, careful and extensive observations have been made. One group (see Table I), consisting of 3 patients in surgical menopause and 4 in natural menopause, was not found to exhibit any particular psychogenic aspect. It is true that 3, in natural climacteric, were somewhat neurotic, but it was found, as Ripley, Shorr and Papanicalaou⁴ observed, that prompt and continued relief from menopausal flushes was obtained with estrogen* (supplemented occasionally with phenobarbital) without affecting the melancholia. Of the remainder, there was no doubt in the minds of the observers that at the outset the patients were in much distress from "suffocations" and flushes, and it was equally clear that complete relief was promptly afforded by the hormone. It is possible, of course, that some psychic or other condition of the patient or her environment may have been corrected consciously or unconsciously by her, her family, or her friends, and that this contributed to the relief which we have ascribed primarily to estrogen. If so, we were unable to bring such factors to light.

In the third group of patients (see Table II), there were 8 in surgical menopause, 2 in irradiation menopause, and 1 who experienced intense flushes premenstrually. This patient had menometrorrhagia, and during a period of previous hospitalization her condition had been diagnosed as dementia precox. While the high lights of the several cases will be seen in Table II, the essential features of two of these may be re-emphasized against a more ample statement of the cases. This group of patients, with the exception of the last, have in common the fact that although each lacked productive ovarian tissue, administration of estrogen either did not relieve the flushes substantially, or continuance of the hormone at a high dosage level did not prevent the recurrence of symptoms if some specific disturbing condition became renewed in the course of treatment. This group is of interest, therefore, because it was found that they presented a psychogenic or other condition as a co-factor, with estrogen deficiency, in the genesis of flushes in induced menopause; they were not merely coincidental accompaniments of the menopause syndrome.

In several of these cases, the role of such a co-factor was forced upon us. Thus, one patient (V. L.) was seen in November, 1939. At that time, flushes were not sufficiently frequent or intense to cause her to be "needled." Two weeks later, she appeared at the clinic of her own volition. At this time she was nervous, excitable, and the victim of flushes which came over her one upon another. Estrogen was given in high dosage, and the patient was instructed to return twice weekly. Flushes became less for a day, but returned with only moderate diminution in intensity for ten days. With continued treatment, there appeared to be satisfactory relief from flushes. About the time this point was reached, a freshly healed scar was noted, as her scarf slipped down, just above the manubrium. It was then learned that her husband had attempted to stab her two days before the flushes had become unbearable. The relief which she sought and we ventured to give with estrogen coincided with court procedures during which her husband was put on probation; the flushes disappeared within a day of the time that relative peace in her home was assured. Estrogen was withdrawn for two months, but it was resumed at the end of this time when the patient returned to the clinic with renewal of intense flushes. This time, however, a bruised eye, broken glasses, and a bandaged forehead testified to the source of her trouble. A single injection of a small amount of estrogen was followed by prompt relief, but this coincided with assurance by the court that her assailant, a relative by marriage, would not be permitted to come in the vicinity of her home. The patient has remained almost free of symptoms since that time, except for moderate flushes, not sufficient to require steady treatment, particularly during the summer months when the patient worked as a domestic servant.

*The hormones used were generously supplied by various concerns, as follows: Abbott Laboratories, estrone and estriol; Ciba Pharmaceutical Products, Inc., estradiol, estradiol-dipropionate and testosterone-propionate; Parke, Davis & Co., estrone; Schering Corporation, estradiol, estradiol-benzoate.

TABLE I. PATIENTS EXPERIENCING RELIEF FROM FLUSHES AND SWEATS, PRIMARILY AS A RESULT OF ESTROGEN

NAME	AGE	MENO-PAUSAL OR CLIMACTERIC STATE	PSYCHOGENIC OR OTHER CONTRIBUTING FACTOR TO THE SYNDROME	REMARKS CONCERNING TREATMENT, CONDITION AND RESPONSE	RESULT OF TREATMENT
H. F.	54	Surgical, 5 years' duration	Nothing found of a specific nature; seems emotionally unstable	Endocrine obesity; headache, backache, arthritis, kraurosis vulvae. Estrogen with occasional phenobarbital gave relief from flushes and sweats.	Flushes relieved. Arthralgia remained. Discharged after 6 months.
A. N.	42	Surgical, 1 month's duration	Job as cashier made her nervous immediately after operation; never did before; flushes became intense at this time, but began the previous summer	Neat appearance, pleasant disposition, and not introspective. Prompt relief with estrogen. Talked of returning to work after one month, returned to work after treatment for 5 months.	Completely relieved of flushes. Discharged after 6 months.
F. W.	42	Surgical, 3 months' duration	States flushes come day and night; cold at night; no psychogenic factor found in observations lasting 6 months	Flushes, sweats, chills come all the time; headache at times and arthralgia. Prompt relief with estrogen, but slight tendency for recurrence in hot weather.	Prompt relief. Discharged after 6 months.
M. M.	47	Natural, 3 years' duration	No psychogenic factor found, although there was illness in family	Chief complaint, flushes and sweats for over a year. Prompt relief with estrogen; no return when house burned or uterine bleeding returned. Moderate flushes with effort of moving.	Prompt relief. Discharged after 7 months.
H. K.	52	Natural, 2 years' duration	Fears high blood pressure. Somewhat melancholic. Continued to suspect high blood pressure even when assured it was not high	Flushes frequent and severe; dizzy, pounding sensation in head, insomnia. Blood pressure 132/75-70; urine negative. Prompt relief from flushes but other symptoms remained.	Relief from flushes; other symptoms remained. Treatment stopped after 3 months.
S. L.	43	Natural, 15 months' duration	Melancholia; no particular factor noted; relief money inadequate for family	Flushes, sweats, chills; headache; kraurosis vulvae, pruritis; insomnia; very susceptible to heat, and shows marked effort syndrome. Prompt relief from flushes with estrogen; phenobarbital for insomnia.	Relief from flushes. Continuing injections, over 7 months.
N. S.	56	Natural, 10 years' duration	Involuntary melancholia with talk of suicide; general debility from undernutrition and diabetes mellitus	Incessant flushes, sweats and chills; insomnia and arthralgia. Estrogen, with phenobarbital periodically, gave much relief.	Relieved of flushes; worries and arthralgia still present. Continuing treatment.

Probably the majority of workers are convinced of the superiority of cultures over smears, but there are still many who feel that the methods are too difficult and impractical for routine use and that cultures can be reliable only if patients can be treated where laboratory facilities for immediate culture are available.

Because of these facts, it was believed that the data on smears and cultures accumulated in our study for the evaluation of therapies were worth reporting. In this study, the patients (all women) have been followed routinely by cultures and smears until they were discharged. A few of the patients were studied at the University of Chicago Lying-in Dispensary, but the great majority of them have been treated at the Chicago Municipal Social Hygiene Clinic* which is about five miles from the laboratory, thirty to forty-five minutes by trolley or elevated train which was the means of transportation used by most of the doctors who assisted in this problem. It was essential, therefore, to use some method of transportation of cultures and culture materials.

PROCEDURES

All necessary equipment, slides, swabs, broth tubes, and plates of media were transported from the laboratory to the Municipal Clinic in specially designed cases of ordinary suitcase size. The materials were left at room temperature until they were returned to the laboratory which was usually about five hours. No special precautions were taken to keep the materials warm during transportation even though the temperature on one occasion at least was -13° F.

In order that smear and culture material might be as comparable as possible, swabs were made with a minimum of cotton so that two could be inserted at the same time into the urethral or cervical canal. One swab was used directly to prepare the smear, the other was placed in a tube containing just sufficient nutrient broth to moisten the swab (0.2 to 0.3 c.c.). Better results were obtained when plates were inoculated with swabs so moistened than when they were used directly. The plates were inoculated as soon as possible, but when the clinic was crowded, it was sometimes two to three hours before materials could be plated. One-half plate was used for the cervical, the other half for the urethral cultures.

Practically all of the media reported in the literature in addition to certain experimental media have been tried in an effort to determine the best media and in the hope of devising a cheaper and simpler one. The results of that study will be reported elsewhere. All diagnostic cases were plated routinely on two media. Suffice it to say that the control media is still McLeod's chocolate agar. At first, media were poured three times a week, then twice, and now for some time they have been prepared but once a week. The method has been entirely satisfactory, provided the plates were stored in the refrigerator in well-covered cans.

The inoculated plates were returned to the laboratory and incubated at 35.5° C. in an atmosphere of about 10 per cent carbon dioxide. Incubator space was limited and so large airtight jars were impractical. One-pound coffee cans of approximate liter capacity which held four plates easily were used instead. The plates were put in the coffee cans and about 100 c.c. of carbon dioxide added from a small tank. The amount was determined by displacement of a measured volume of water. Plates were read at the end of 24, 48, and 72 hours. During the warm months of the year about 90 per cent of the cultures grew out in 24 hours, but during the colder months most strains required 48 hours. The number of strains which did not grow out until 72 hours was large enough to make incubation for the extra 24 hours necessary.

*These patients were made available through the Chicago Board of Health, Herman N. Bundesen, President, and Dr. G. G. Taylor, Director of Syphilis and Gonorrhea Section.

TABLE II. PATIENTS EXPERIENCING RELIEF FROM THE MENOPAUSE SYNDROME LARGELY AS A RESULT OF CORRECTING A PSYCHOGENIC, SOCIAL OR MEDICAL PROBLEM

NAME	AGE	MENOPAU- AL OR CLIM- ACTERIC STATE	PSYCHOGENIC OR OTHER CONTRIBUTING FACTOR TO THE SYNDROME	REMARKS CONCERNING TREATMENT, CONDITION AND RESPONSE	RESULT OF TREATMENT
V. L.	27	Surgical, 11 months' duration	Flushes and sweats occur at irregular intervals; severe. Two such periods occurred when attacked and cut by husband and when injured in a brawl.	Estrogen gave prompt relief, but this was found to coincide with settling poor home situations in court. Some return of flushes when work was resumed and weather was hot.	Relieved except when recurrent exciting circumstances arise. These cause complete return of symptoms, despite level of estrogen dosage. Requires additional treatment. Returned to housework.
D. T.	39	Surgical, 7 months' duration	Flushes, sweats, chills, weakness and trembling occurred on certain days at irregular intervals, almost not at all on others. Found to begin in middle of night. Excessive libido; fears softening of brain as result from masturbation.	Little improvement with estrogen. Complete relief after four days when assured masturbation was not physically harmful, in moderation. Estrogens withdrawn after two weeks; no return of flushes.	Completely relieved of flushes and nervousness. Noted dryness of skin and increased amount of urine; this caused some return of symptoms, but these subsided when situation was explained. Stopped coming to clinic, although seen to be well at later times.
D. M.	38	Surgical, 2 months' duration	Flushes, sweats, result of change in social status after husband lost job. Difficulty with children. Noted ankles and eyes swollen at about two-week intervals; coincided with three to four days before next relief check. Worried over bed-wetting habit of seven-year-old daughter.	Very prompt relief when medical aid was given child; diet was supplemented with money for better diet. Recurrence of flushes when husband was put off VPA, and when uterine bleeding recurred.	Relieved, except for occasional intervals when recurrence of home troubles worries her. Then flushes return, despite high estrogen dosage.
J. N.	44	Surgical, 1 year's du- ration	Flushes and sweats very strong in early afternoon, continue into night; not much troubled in morning. Noted that they commence during lunch hour when she whips son who does not read and will not study (9 years old, third year in first grade). Both anticipate this. Boy was breech, required artificial respiration and "had head operated," soon after birth. Worried also over lack of work.	Very little improvement with estrogen. After nature of case was understood, was advised to refrain from making trouble with son. After two months situation was better. Patient looked well and was nearly relieved of flushes. Secured work again and is still well. Flushes come with hard work and eating meat.	Much improved; treatment withdrawn when patient returned to work.

Another case in which relief of flushes was even more certainly ascribable to removal of a neurosis was that of D. T., a negress, 39 years of age. She was formerly married, but now lived with her mother; both gave the impression of being outwardly religious, and read books on character improvement. The patient was, in her own words, "extremely passionate." Her complaint was that of flushes, drenching sweats, trembling, weakness, and headaches. Some days were free of symptoms, but more often were incessantly present. With estrogen, the intensity of the flushes lessened somewhat, but not the frequency. It was then noted that they commenced, on the troubled days, in the early morning hours, and continued thereafter for an indefinite period. Phenobarbital was without effect. About this time (after two and one-half weeks of intensive estrogen therapy), the patient confided the fact that the only relief she could obtain was from repeated masturbation, but this, she had been told by friends, would cause "softening of the brain." The conflict, which had existed long before bilateral ovariectomy and hysterectomy seven months previously, failed in the presence of the ovary to bring on any physiologic changes typical of the menopause syndrome. Soon after the operation, however, the ovarian deficiency was clearly a co-factor in the syndrome. Since the flushes and their attendant sequelae were promptly relieved within four days after the patient was assured that masturbation would not lead to the consequences which she feared, and since estrogen was of little use at the outset, it is clear that the symptomatology of this instance of surgical menopause resulted from both *hormonic* and *psychogenic* factors.

The extent of, and basis for, relief from menopausal flushes in the remaining cases of this series may be seen in Table II. In each, it is ascribable to correction of a psychogenic factor, and in one (D. M.) this was coupled with periodic nutritional deficiency which dietary care corrected very promptly. The neuroses with which it was necessary to deal ranged from child-parent conflicts of specific sorts (D. M., J. N., E. M., C. O.) and cancerphobia (R. W.) to various types of melancholia, most often attributable to insufficient money or to social maladjustment (M. D., E. M., M. diL., R. W., J. N.). One was clearly a case of insanity (F. B.) in whom appropriate suggestion alleviated the flushes, it was said. One (E. P.) appears to have been solely a case of poor physical condition, largely resulting from poor eating habits and from unwise use of laxatives.

COMMENT

All in all, therefore, it is clear from the above account that in these instances of induced menopause (10 out of 13 listed in Tables I and II), estrogen alone, or combined with phenobarbital, was without important effect on the purely objective vasomotor phenomena in which we were interested. This was so since neuroses or other conditions of various sorts were present as contributing, rather than coincidental, factors. The mechanism by which nervous elements modify the state of the smallest blood vessels of the skin remains to be defined.

The fact that psychogenic factors may bear a causal relation to the flushes of the surgical menopause suggests several pertinent questions. Why is it, one would like to know, that a neurosis in the presence of normally functioning ovaries does not give rise to the vasomotor disturbances of the menopause, but soon after ovarian deprivation, typical vascular symptoms may appear in intense, aggravated form? Or again, at what level in the brain stem is this wave of vasodilatation of the skin blood vessels with attendant sensation of heat and suffocation set into action? And finally, for what functional change in nerves, skin, or tissues in general does the menopausal flush "compensate" at such an expense of comfort to the patient, and frequently with such inefficiency that the flush is followed by vasoconstriction and an equally uncomfortable sensation of coldness?

To answer these questions, much further work will be required. This will take into account a number of facts, some of which are generally recognized by clinicians while others have only recently been acquired in laboratory studies. For example, the flush is usually observed to accompany several basic conditions: excitement, emotion, exercise, and, sometimes, eating. These, it may be observed, are conditions which measurably increase heat-production by the body, or which affect the mechanisms of heat-loss by the body. Moreover, flushes tend to be more frequent and more intense in some women during warm weather, or at times when they are resting, but fully covered by bed clothes. Such considerations as these suggest either that the menopausal woman is essentially deficient in mechanisms for losing heat easily, or that the centers for regulation of heat-loss by the body may be unduly sensitive to otherwise inadequate stimuli. It, therefore, follows that estrogen, sedatives or correction of neuroses, alone or combined with other therapeutic measures, may be effective in alleviation of the vasomotor menopausal disturbances through the action which they have in facilitating adequate and normal circulation of blood in the skin. The extent to which this is achieved by peripheral circulatory adjustments may be shown by suitable studies, whereas the central effects which therapeutic measures possess would appear to be at the level of the brain stem at which temperature-regulating centers are located. This would point, therefore, to the hypothalamus as the seat,^{1, 2} or focus, upon which psychogenic or other bodily influences play, directly or indirectly, with such mischief after surgical removal of the ovaries in women.

SUMMARY

Intensive study was made of a group of eighteen women whose primary complaint was strong, frequent menopausal flushes. Thirteen patients were in artificial menopause, 4 were in natural menopause, and 1 was still menstruating. The patients were divided into two groups, according to the way in which they responded to treatment. Seven (3 in surgical menopause, 4 in natural menopause) responded immediately and well to estrogen therapy, so far as subsidence of the flushes was concerned. Of the remaining 11, 10 were in artificial menopause, 1 was still menstruating. These patients did not respond well to estrogen (or phenobarbital) therapy, but either responded well to correction of a neurosis or other medical problem, or they exhibited signs of such complicating factors with which it was not feasible or possible to deal. In view of currently held beliefs that the most common aspect of the surgical menopause is vasomotor instability without important psychogenic factors, the results recorded in this study are held to be significant. Elucidation of a psychogenic factor as a contributing, and not merely coincidental, factor to the flush of the surgical menopause was possible only in view of the extensive, special study which these patients received.

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E. M.	51	Surgical, 2 months' duration	Flushes, sweats, and especially chills to the bone. Hard winters in a cold water flat; grown son will not work. Moderately depressed.	Much relief with estrogen. Never for more than two to three weeks. No success in helping home situation.	Intermittent relief only; marked exacerbation of symptoms at two- to three-week intervals.
C. O.	26	Surgical, 2 months' duration	Difficulty in feeding child; husband unable to work, but unable to obtain relief; apparently kept in state of high tension by interference of mother.	After three months' high estrogen therapy, good results were intermittently obtained as difficulties were intermittently less. Best relief in summer, when mother goes to beach.	Intermittent relief, despite estrogen, until summer when afforded fairly continuous relief from flushes. Symptoms ceased as son attended kindergarten. Estrogen withdrawn after eight months.
R. W.	46	Irradiation, 2 years' duration	Flushes, sweats, and severe arthralgia; involutional melancholia; fear of cancer (associates irradiation of ovaries for menorrhagia with malignancy). Talked much of death and futility of living.	Marked improvement in ten days; estrogen probably helpful, but assurance regarding cancer and physical therapy for arthralgia made a new personality. Libido returned.	Relief from menopausal symptoms, but continued treatment for three months after cessation of flushes. Estrogen withdrawn after nine months.
M. diL.	45	Irradiation, 5 years' duration	Flushes, sweats, chills, anorexia, melancholia; weakness; arthralgia; undernourished and constipated.	Estrogen, with phenobarbital, brought little relief. Advised regarding more adequate diet and withdrawing cathartics. Advised to do more for grandchild.	Moderate and intermittent relief only with continued estrogen.
M. D.	45	Surgical, 3 years' duration	Complete menopause syndrome including melancholia and anorexia. Particularly oppressed and agitated by relief investigator, who thinks patient should work. Outwardly placid, but feels "suffocated" and afraid of people.	Relief from flushes in three weeks. Recurred with induced menstruation and especially with visit of investigator. Relief finally attained when patient went to live with people for whom she formerly worked.	Relieved of flushes temporarily. Requires intermittent treatment.
F. B.	39	Intense menometrorrhagia	Marked premenstrual tension with flushes. Strong libido, desires to hold man, fears pregnancy. Desires artificial menopause. Unable to work due to menorrhagia.	No relief with estrogens or androgens. With assurance of dilatation and curettage and possible ovarian irradiation, prompt relief.	Relieved of flushes. Previous diagnosis on observation in hospital, dementia precox.
E. P.	37	Surgical, 1 year's duration	No specific thing found. Anorexia; piles and hemorrhoids; uses strong cathartics excessively and enemas one to three times weekly.	Advised on diet, and against cathartics. Received but 2 injections of estrogen in one week. Seen in clinic later, reported flushes gone.	Claimed relief from flushes.

STATISTICS

In ten years 330 sections were performed in a total number of 5,628 obstetric deliveries, an incidence of 5.8 per cent, or of 1 section in every 17 deliveries.

Of these 330 sections, about 70 per cent were primary, 26 per cent secondary, 3 per cent third sections, and 4, or 1 per cent, fourth sections.

Among the 330, 244, or about 74 per cent, were elective, that is, performed before labor; and 86, or 26 per cent, were performed after labor had started, instead of about three-fourths elective and one-fourth otherwise.

Again, of the 330, 218, or 66 per cent, were classical sections; 100, or 30 per cent, were low-flap sections; 5 were Latzko; 1 was vaginal; and in 6 the type was not disclosed from the records.

The indications for these 330 sections, as given by the operators, not being germane to the discussion, will be dismissed with the statement that about 30 per cent were performed because of previous sections, and 27 per cent because of abnormal pelves, about 8 per cent for previas, and 7 per cent for prolonged labors with little progress; these 4 indications constituted about 72 per cent or nearly three-fourths of all the indications.

The morbidity (temperatures of 100.6° F. for forty-eight hours exclusive of the first twenty-four hours), following these 330 sections, was 63, or 19 per cent. The morbidity of puerperal origin was 55, or 16.6 per cent, and that of nonpuerperal origin was 8, or 2.4 per cent. In this discussion, the puerperal morbidity only will be considered.

The puerperal morbidity following the 244 elective sections was 13.5 per cent; while following the 86 sections performed after labor had started, it was 25.5 per cent, considerably higher as might be expected.

The puerperal morbidity following the 218 classical sections was 12.38 per cent. After the 100 low-flap sections it was 24 per cent, almost twice as high. After the 5 Latzko sections it was 40 per cent. After the 1 vaginal section, there was no puerperal morbidity; and after the 6 with type not stated, 2 women showed puerperal morbidity.

Thus, it is seen that following all of the classical and all of the low-flap sections, the puerperal morbidity was about twice as high in the latter, the low-flap section. This, however, is not conclusive, as it is necessary to know how many elective sections and how many performed in labor were in each type of operation.

In the whole 244 elective sections, 173 were classical and 66 were of the low-flap variety. In 5 the type was not stated. The puerperal morbidity following the 173 sections of the classical type was 10.4 per cent; that following the 66 elective sections of the low-flap type was 19.7 per cent, this percentage again being almost twice as high in the low-flap type. (In the 5 elective sections, the type of which was not known, 2 women showed puerperal morbidity.)

Of all the 86 sections performed after labor had begun, 44 were classical, 35 low-flap, 5 Latzko, 1 vaginal, and in 1 the type was not known. The puerperal morbidity following the 44 sections performed in labor of the classical type was 22.7 per cent; that following the 35 performed in labor of the low-flap type was 31.4 per cent, considerably higher. (Following the 5 Latzko operations, it was 2, or 40 per cent. No morbidity followed the vaginal section or the 1 with type not known.)

Thus, the résumé of puerperal morbidity following classical and low-flap sections shows:

In all classical and all low-flap sections, the puerperal morbidity was 12.38 per cent for the former and 24 per cent for the latter, about twice as high in the low-flap section.

In elective sections of the classical type, the puerperal morbidity was 10.4 per cent. In elective sections of the low-flap type, it was 19.7 per cent, again almost twice as high in the low-flap section.

In sections performed in labor of the classical type, the puerperal morbidity was 22.7 per cent. In sections performed in labor of the low-flap type, the puerperal morbidity was 31.4 per cent, almost one-third higher in the low-flap type.

To remove all doubts as to these results, if the 6 sections, the type of which is not known, are all added to the group of classical sections, the relative percentages

A COMPARISON OF THE CLASSICAL AND LOWER SEGMENT CESAREAN SECTION*

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ON SEVERAL occasions in this Society, and from time to time in the medical journals, the statement has been made that the low-flap variety of section gives better results than does the classical.

The claim to better results rests chiefly on three points, a lower puerperal morbidity, a lower maternal mortality and a lower incidence of uterine rupture in subsequent pregnancies.

It is probable that, throughout this country, the total number of classical sections performed is greater than the total number of low-flap sections. Therefore, it is unquestionably true that following all classical sections, there have been more women showing puerperal morbidity, more maternal deaths, and more uterine ruptures in subsequent pregnancies than have been found following all low-flap sections. But have the percentages been higher?

If we assume for the sake of argument, that classical sections outnumber low-flap sections in the ratio of two to one, then the number of women showing puerperal morbidity, the number dying, and the number sustaining uterine rupture in subsequent pregnancies, should be twice as great following classical sections as following low-flap sections, in order that the percentages should be the same. And in order that the percentages should be higher, the total number of these untoward happenings should be not just twice as high but over twice as high.

To me it has seemed possible that the total numbers of these unfortunate consequences of section have been confused with their percentages by those comparing the results of the two types of operation.

Moreover, the classical section antedates the low-flap section by many years, and numerous classical sections have been performed at a period of time when surgery was in a comparatively low state of development. Hence, the results of these early classical sections were less satisfactory.

To arrive, therefore, at a just basis of comparison between the results obtained by classical and low-flap sections, a relatively recent period of time should be selected; and the percentages of results should be estimated from the total number of operations performed by each method.

With this purpose in view, a study has been made of all the sections performed in the Doctors Hospital during the first ten years of its operation. These statistics were compiled from the records by the obstetric resident, Dr. Dean Pinney, from March, 1930, when the hospital opened, to March, 1940.

*Read at a meeting of the New York Obstetrical Society, February 11, 1941.

The second death following a classical section, done after labor had started, was the result of hemorrhage and shock. The operation was performed after many hours of labor. There was profuse bleeding. A transfusion of 500 c.c. of blood proved to be insufficient. Before a second transfusion could be given, the patient died. There is no reason to believe that the result would have been different if the low-flap method had been used.

Both deaths following low-flap sections, performed many hours after artificial rupture of the membranes, resulted from sepsis. The results would probably have been the same had classical sections been performed.

It is possibly significant and but fair to state that the only deaths from sepsis occurred after the low-flap type of section.

Rupture of the uterus in subsequent pregnancies following sections did not occur at all during the ten-year period in the Doctors Hospital.

Thus, it is seen that in this ten-year period at the Doctors Hospital, in the 330 sections performed, the results from the low-flap sections have not been better than those from the classical. On the contrary, in this comparatively small group, results from the classical have been better. The puerperal morbidity following the classical has been much less; the maternal mortality much less; and rupture of the uterus in subsequent pregnancies was the same, that is, it was absent in both types.

No attempt is made in this paper to prove that the classical section gives better results than the low-flap section. Proof cannot be made from such a small group of cases. But the evidence is here given that in one hospital, in a ten-year period, with sections performed by many different operators under similar conditions, results following the classical have on the whole been better. True statistics will always add to the sum total of knowledge.

The purpose of this paper, as mentioned, is not to try to settle the question of the superiority of one type over the other, but to submit this evidence in the hope that other observers will be encouraged to give additional information in more and larger groups of sections.

If the low-flap section cannot be shown definitely to give better results than the classical, then it would seem that it should not be given the preference. For the low-flap operation is more difficult to perform. It takes longer. It is usually attended with more bleeding. It carries greater danger of bladder injury. In transverse incisions into the uterus, there is danger of extension into the broad ligaments during delivery. In placenta previa the incision is often made directly into the placental site, in the thinned-out portion of the uterus where hemorrhage is hard to control; while in the classical, the incision may avoid the placental site entirely.

The low-flap type has one advantage over the classical, in that the baby may be delivered by the vertex instead of by breech. This advantage disappears, however, when section is performed for breech presentation.

In short, in the absence of proof to the contrary, the classical would seem to be the better operation. It is easier, quicker, with bleeding under better control, and it carries less danger of damage to surrounding tissues.

For the highly skilled gynecologist, the low-flap section will give good results (possibly no better than the classical). For the great mass of obstetricians throughout the country, many of whom do safe, conserva-

will be changed but slightly. Five of these were elective sections, 2 showing puerperal morbidity. The sixth done in labor showed no morbidity. If these 5 elective sections are all classed with the 173 known elective sections of classical type, the puerperal morbidity will be 11.5 per cent instead of 10.4 per cent as given above. This would still be much lower than the puerperal morbidity of 19.7 per cent, following the elective sections of the low-flap type.

The conclusion, therefore, is that low-flap sections were followed by a higher puerperal morbidity than were the classical in those performed before labor, in electives, in those performed after labor had begun, and in all considered together, in a survey of all the sections performed in ten years by many different operators at the Doctors Hospital.

Maternal deaths following the 330 sections, happily for the Doctors Hospital and unfortunately for comparative statistics, were so few that no real conclusions can be formed concerning the relative merits of the classical and low-flap sections on this basis. But so far as it goes, the advantage is with the classical. In the whole 330 sections, the maternal mortality was 4, or 1.2 per cent, 12 per 1,000.

There was only 1 death in the 244 elective sections, a mortality of 0.41 per cent, or of 4.1 per 1,000. In the 86 sections performed after labor had started, there were 3 deaths, a mortality of 3.45 per cent, or of 34.5 per 1,000, more than 8 times higher. All of these 4 deaths occurred in the known classical or low-flap sections. None occurred in the 5 Latzko, the 1 vaginal, or in the 6 of unknown type.

In the whole 218 classical sections, there were 2 deaths, a mortality of a little less than 1 per cent, 0.97 per cent, or of 9.7 per 1,000. In all of the 100 low-flap sections, there were also 2 deaths, a mortality of 2 per cent, or of 20 per 1,000, over twice that in the classical.

In the 173 elective sections of the classical type, there was 1 death, a mortality of 0.58 per cent, or of 5.8 per 1,000. In the 86 elective sections of the low-flap type there was no death.

In the 44 sections performed in labor of the classical type, there was 1 death, a mortality of 2.27 per cent or of 22.7 per 1,000. In the 35 sections performed in labor by the low-flap method, 2 deaths occurred, giving a mortality of 5.71 per cent, or of 57.1 per 1,000, a mortality two and one-half times higher in the low-flap type.

SUMMARY AND CONCLUSIONS

Thus, the maternal mortality following all low-flap sections was twice as high as that following all classical sections.

In sections performed after labor had begun, the maternal mortality following those done by the low-flap method was two and one-half times higher than those done by the classical method.

In elective sections alone was the mortality less after the low-flap type of section.

However, as has been said, the total number of maternal deaths was so low that conclusions from them cannot be very convincing. And also when the causes of these deaths are studied, a candid opinion must be that the type of section had little to do with the results.

In the whole 330 sections, the only death after an elective operation, performed by the classical method, seemed entirely independent of the type of section employed. The patient was a mental case who jumped out of bed shortly after being returned to her room. Disruption of the abdominal wound resulted. This in turn caused an intestinal obstruction from which she died, operation for relief being too late. This unfortunate result could not have been due to the manner in which the uterus was opened and closed, as the disruption was in the abdominal wound. In my own series of private sections, the only disruption of an abdominal wound occurred following a low-flap operation.

DISCUSSION

DR. GEORGE W. KOSMAK.—Discussions on the comparative efficacy and value of certain obstetric procedures are no more out of line than those witnessed in other fields of medicine. As cesarean sections became more universal, different techniques found adherents, just as in gastrointestinal, prostatic, biliary, brain, thyroid, and other surgical realms. The antagonisms between the urologist who preferred perineal to suprapubic proctectomy, or the general surgeon who condemned cholecystotomy in contrast to cholecystectomy, are by no means adjusted. A similar relegation to the discard has been attempted by those in the low-flap group of "cesareanists," to coin a word. As a matter of fact some of our outstanding obstetric operators have been most disdainful in their comments leveled at those who favored the classical operation. One need only note the caustic remarks in successive editions of the admirable *Year Book on Obstetrics*. It would appear as if the man who did otherwise than a "low flap" was committing a crime.

A carefully studied paper like that of Dr. Ryder constitutes a relief to those who want to be impartial, who are desirous of being guided in their decisions by the final results on patients rather than by the bright and dazzling light of the propagandist for a particular procedure.

Let us look at the record. Dr. Ryder has favored us with a carefully elaborated set of statistics from a hospital of special character in which a cross section of the New York profession, specialist and otherwise, cares for a group of higher income class bracket patients. This may or may not have a bearing on results. However, an incidence of 5.8 per cent, or 1 in every 17 deliveries, impresses one as rather high when compared with the so-called lower income group in our municipal hospitals. This is not intended as a reflection on more conservative indications, but the fact that previous section was done in almost 30 per cent of the patients, must be taken into account in the final decision. Other indications, aside from abnormal pelvis, constituted a minority in the final analysis. It is of interest to note, however, that the classical operation was done in 66 per cent and the low-flap operation in 30 per cent of the cases, with about 12½ per cent morbidity in the former and 24 per cent in the latter. If we differentiate between elective and in labor operations, the results again favor the classical procedure. As there were only 4 maternal deaths, two for each type, this factor can be eliminated. Based on the morbidity results, therefore, one cannot disagree with Dr. Ryder's assertion that the classical operation essentially is superior for the type of patient and the type of operator concerned in this service.

There may be no question of course, as Dr. Ryder has shown, that the classical operation in his series, is superior so far as simplicity and final results are concerned. But it will not settle the choice, for operators will continue to be guided by their personal preference. However, his presentation will, if studied carefully, detract somewhat from the laudatory encomiums which have been lavished by enthusiastic proponents upon the newer procedure. An important point, which cannot be set aside, is that cesarean section is a matter of early deliberation and execution rather than a last resort indication. The elements which must be fully considered are hemorrhage, shock, and sepsis and these, if present, are all included in the general designation of morbidity. I believe that a mere rise of temperature should not be regarded as the only item in determining a satisfactory recovery of the patients, and it would have been of interest if we knew how long they had to be kept in bed, the character of the puerperium, complicating conditions, such as anemia, behavior of bladder, and bowels, and a general restoration to health. These would constitute better criteria than a little fever, and we should look forward to an analysis from this point of view.

Personally, I believe that the upper uterine segment is safer for incision than the lower, that the so-called dangerous uterine spill can be avoided, that hemorrhage may be better controlled, the fetus and placenta more readily extracted and, if tubal sterilization is indicated, that it can more easily be carried out. However, I doubt whether either group of operators can be swayed from their position, and if each claims their approach is preferable, they can readily bring statistics to their support. There is always value, however, in controversy; it does prevent the development of too high a degree of self-assurance.

tive, skillful, and satisfactory work, the classical section, in all probability, should give better results than the low-flap section.

In any large series of obstetric deliveries, especially among the upper classes and in this country with its mixed population, Cesarean section is going to be necessary at times, whether the incidence is 2, 4, or 6 per cent. Men well qualified to do 95 per cent of the deliveries will occasionally be confronted with the necessity of doing the remaining 5 per cent by section. Why should they not employ the easiest type of section, the classical, unless the low-flap type is shown to be better?

If the low-flap section were extraperitoneal, the argument for its general use would be stronger. In neglected cases, or in those where labor for various reasons has continued for unduly long periods of time, the Latzko or similar operations, being extraperitoneal, should give the best results. These operations are necessary, however, probably in less than $\frac{1}{2}$ per cent of all obstetric deliveries.

It would seem logical, unless there is proof to the contrary, that the best results might be obtained by the employment of the classical section for general use, supplemented by the Latzko or allied extraperitoneal operations, for the neglected or occasional case.

In closing, may further attention be called to this series of 330 sections which presumably represents a fair cross section of private practice in the better hospitals.

Elective sections were about 3 times as frequent as those performed after labor had begun.

Puerperal morbidity following elective sections was much lower than that following sections performed in labor, 13.5 per cent in contrast to 25.5 per cent.

Maternal mortality, from all causes, following elective sections was 8 times less than that following sections performed after labor had started.

Following 5 Latzko sections, in infected or potentially infected cases, there was no maternal mortality.

Maternal mortality following sections was 9 times higher than that following pelvic deliveries, 1.2 per cent for the former and 0.13 per cent for the latter; in a total maternal mortality of 0.19 per cent in 5,628 deliveries.

From these statistics, three obvious conclusions may be drawn, and a fourth, the point of discussion in this paper, is added:

1. Sections should never be decided upon in the absence of very strong indications, as the maternal mortality is much higher than in pelvic deliveries.

2. It is much better, where possible, to decide upon and to perform section in advance of labor, as the maternal mortality is much less than in sections performed after labor has started and has progressed for hours.

3. Where labor has been in progress for an undue length of time and section is found necessary, extraperitoneal section is the safest.

4. During a ten-year service at the Doctors Hospital, in an admittedly small number of cases, results from the classical section have been better, on the whole, than those from the low-flap section.

Usually colonies could be detected by direct inspection, but the oxydase test was used routinely for confirmation and as an aid in picking colonies from badly overgrown plates. Tetramethyl-p-phenylenediamine hydrochloride was used in preference to the dimethyl compound, because it did not kill the gonococcus, and with it, the gentian violet color appeared almost instantly as compared with one or two minutes when the dimethyl compound was used. Most workers seem to use the dimethyl compound in spite of its disadvantages because of the difference in price of the two compounds. Actually, the amount of material required is so small that price hardly needs to be considered. It is important that the solution be prepared fresh daily and, of course, if it were necessary to weigh out sufficient material to give an accurate 1 per cent solution, the expense might be great. A small amount of crystalline material about 0.5 cm. sq. heaped on the end of a spatula is sufficient for 10 c.c. of distilled water and that amount of solution is enough for 50 plates. The plates need not be sprayed with the reagent. One drop of solution is sufficient to confirm a suspicious colony, and three to four drops will moisten the surface of a heavily overgrown plate. For isolation it is better to pick colonies which have not been contaminated by the solution. An attempt was made to isolate as many strains as possible for future study. All strains isolated have been confirmed by fermentation tests.

NUMBER AND SOURCE OF SPECIMENS

Two hundred and sixteen patients have been considered in this study. It includes only patients in whom a diagnosis was made on the basis of isolation of the gonococcus and whose treatment was followed and cure determined by cultures. The number of cultures per patient varied from 3 to 32; the minimum for any patient discharged has been 17. One thousand six hundred and fifty-six cervical and 1,675 urethral smears and cultures have been compared. Only satisfactory smears and cultures have been included; i.e., if the culture was so badly overgrown as to be doubtful or if the smear was too thin or contaminated to be read (204 specimens), these reports have been deleted.

The reliability of initial diagnosis or of cure whether on the basis of smear or culture is largely dependent upon the technique used in the collection of material. Good smears are unquestionably more difficult to obtain in women than in men, but with care they can be prepared quite easily. It is important that the material be taken from sites which harbor the gonococcus, namely Skene's, Bartholin's, and endocervical glands. Material from the vagina or the vaginal introitus rarely contains gonococci after subsidence of the acute stage of the infection. Moreover, material from this area is usually so badly contaminated with vaginal bacteria that the slides are unreadable, and the cultures are overgrown.

The meatus of the urethra should be wiped dry with a piece of cotton to avoid inclusion of confusing vulvar bacteria. The finger should then be passed within the vagina, and the urethra firmly stripped from above downward against the pubic arch. A cotton swab or platinum needle may be used for collection of the material.

In order to obtain satisfactory specimens from the cervical glands, the cervix should be exposed with a speculum which has been inserted without lubrication other than water. The vaginal secretion should be wiped out and the plug of cervical mucus mechanically removed. The cervix should then be compressed with the speculum in order to force the secretion from the endocervical glands, and the material removed on a cotton swab inserted directly into the cervical canal. Some workers prefer to insert the swab and then compress the cervix.

RESULTS

The importance of cultures in the determination of cure can best be demonstrated by a few representative charts of patients on local treatment. Occasionally an erratic positive culture preceded and followed by negative cultures showed that the patient still harbored the organism although smears were never positive. These positive cultures frequently appeared during and just following the menstrual period.

DR. HENRY T. BURNS.—About twelve years ago when the low-flap procedure was gaining popularity rapidly, I did a few and found it took from ten to fifteen minutes longer than the classical section. I observed many other men doing the low-flap cesarean section, and I felt that the anesthesia longer by fifteen minutes and exposure of the abdomen, counterbalanced the good effects that may be obtained by opening the lower uterine segment. I gave up the low-flap operation about ten years ago and have not done it since.

I do two types of low cesarean section and by that I mean making an incision in the abdominal wall as low, I think, as those using the low-flap operation, just above the bladder. In the majority of my cases I do not see the intestines, and I do not feel that much of the spill goes above the broad ligaments because I operate on my patients in the flat rather than in the Trendelenburg position.

The other type is a true extraperitoneal section, the Latzko type of operation, of which I have done 59. In addition I have done 5 by the Waters' technique making a total of 64 true extraperitoneal type of operation, without a maternal death.

DR. BENJAMIN P. WATSON.—The great object in the low-flap procedure is to prevent spill into the abdominal cavity. I have seen many low-flap operations done in which there was just as much spill as in the classical operation.

In an elective cesarean section on a patient who has not been in labor, it is not always easy to get a sufficient flap of peritoneum raised from the lower uterine segment absolutely to shut off the upper peritoneal cavity from spill. The technical difficulty of pushing the bladder down, raising the upper flap and attaching the flap, as it should be attached, may be great, so that trauma may be inflicted upon the connective tissue. Therefore, in doing cesarean section at the time of election, where the patient has not been in labor, I believe that a low classical section will give just as good results as the low-flap section to the experienced operator and better results to the occasional operator. On the other hand, if the patient has been in labor for some time, if the lower uterine segment has been pulled up and the bladder has been pulled up, the low-flap procedure is very much easier. You can get better flaps and you can shut off the upper peritoneal cavity completely. Under those circumstances, the low-flap operation is the better procedure.

With respect to the danger of subsequent rupture of the uterus, I do not believe that there is less danger after the low-flap section than there is after the classical operation, provided the uterine wall is stitched in the proper way when the classical section is done.

DR. EDWARD G. WATERS.—The vast majority of papers on cesarean section in the past ten years seem to indicate that any type of low-flap operation is better by almost any standard than the old classical operation. If a low-flap operation is better in potentially infected cases then it should be a still better operation in clean cases.

At the Margaret Hague Maternity, about 70 per cent of the cesarean sections are of the low-flap transperitoneal type, because it is our experience that these are safer operations, judged by standards of morbidity, mortality, patient's comfort, and operative hazards. We are well acquainted with all of the hackneyed objections to the low-flap operation and the low transverse cervical incision, and have concluded, in an experience of about 1,500 sections, that they exist mainly in the minds of those who do not perform operations of this type.

We have yet to see an actual intra-partum rupture of the uterus where the low transverse cervical incision had been used, despite the fact that 70 per cent of our cases are of that type. Although only about 10 per cent of our cases are classical sections, we have seen five cases of uterine rupture (in a group of 25 ruptured uteri) follow previous classical section. Rupture of the uterus through a low-placed scar must be very rare by comparison with data on classical scars.

Our statistics for a period of four years (1937, 1938, 1939, and 1940), which is a comparable time to Dr. Ryder's carefully analyzed group, show during that period, that there were 21,862 deliveries, of which 737 were delivered by cesarean section, an incidence of 3.3 per cent; about half the incidence reported here tonight. There were 9 deaths, a mortality rate of 1.2 per cent, which is exactly the same as quoted by Dr. Ryder for his group. Those 9 might be corrected down to a group of 4,

where the fault lay with the type of operation performed. The other 5 patients would have died with or without operation, and irrespective of the type done. There were only 35 classical sections, an incidence of 4.7 per cent, done mainly on patients in whom it was felt that no further pregnancy should be permitted and who should be sterilized. There were 3 deaths in the classical section group, a mortality of 8.5 per cent. It may be that we do classical sections so seldom that we no longer know how to do them.

There were 511 low segment operations, an incidence of 69.3 per cent, and in this group there were 4 deaths, a mortality rate of 0.08 per cent.

There were 181 extraperitoneal operations, an incidence of 24.6 per cent, with one death, or 0.5 per cent. These sections were done in potentially and actually infected patients. In this group there were 7 cesarean hysterectomies, an incidence of 0.9 per cent, with no deaths.

Even with a group of 737 cesarean sections, it is very important to remember that percentages do not mean much, for one or two deaths can markedly alter mortality rates. For example, I think the percentage of deaths which Dr. Ryder quoted in the low transperitoneal operation was about 7 per cent in a group of about 66. To judge the value of an operation from the mortality standpoint, the series of cases must be in the thousands to mean much.

DR. RALPH L. BARRETT.—It is all very well to report that the classical section is satisfactory, as in this series. That is true, but if all the series are considered together for the last fifteen years, three series of over 200 or 300 cases in which the classical operation can be shown to have as good a mortality rate as the low-flap operation cannot be found. In general, the low-flap procedure will show less than half the mortality rate of the classical section. We tried it out at the Woman's Hospital on 1,000 cases which were reported before this Society, where the mortality has been cut down in the low-flap operation to five-tenths of one per cent from all causes.

There are some of us who feel very strongly about the low-flap section. We believe that, if it is better for the woman who has been in labor, it is equally good for the woman who has not been in labor.

DR. CLAUDE E. HEATON.—On Dr. Holden's service at the French Hospital which began in April, 1935, there were during the first four years 3,103 deliveries. In this series 125 cesarean sections were performed, a rate of 4 per cent. The operations were done by 22 operators, but about 6 of these operators did 90 per cent of the cases. There were 73 classical operations, 45 low-flap operations, 6 Latzko operations, and 1 peritoneal excision. The morbidity for the classical type was 28 per cent; for the low-flap section 26 per cent, and for the extraperitoneal type 50 per cent on the basis of 100° F. One patient died, after a low-flap operation done under local anesthesia for progressive toxemia, of cerebral hemorrhage twenty hours after operation. This gives a mortality rate of 0.80 per cent.

DR. INGLIS F. FROST.—Following the classical operation, adhesions are more likely to occur than in the low-flap procedure. If, in a secondary cesarean operation, adhesions are present, real difficulty may be encountered, especially is this true if these adhesions are marked in the region of the uterine scar. They may also interfere with normal uterine contraction following delivery.

DR. HERVEY C. WILLIAMSON.—The low-flap section is not a difficult operation but just as simple as the classical operation, the only difference being that a few moments must be taken to dissect the flaps and a few more to close them after the uterus is sutured. I have never observed that the low-flap operation caused more bleeding than the classical operation, rather definitely less, especially when local anesthesia is used.

DR. HARRY ARANOW.—I feel much safer in doing the low-flap operation, and after you have trained a group of men to do that particular type of operation, it is not very difficult. I do not think that time is such an important element, whether it be five minutes more or less.

DR. RYDER (closing).—Of those taking part in this discussion, four expressed preference for the classical type of section and five for the low-flap type. I expected the preference to be more decidedly in favor of the low-flap type.

I have examined over 27 recent articles on cesarean section, and in all but one, the preference was in favor of the low-flap type. However, in all of these articles, statistics were lacking to substantiate the preference.

In the November, 1940, number of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, there appeared an article by Dr. King of New Orleans. In the discussion following, Dr. Falls of Chicago said that he had performed 200 sections in his service alternately by the classical and low-flap methods and that his results were practically identical. This is the only instance found, in the 27 articles read, where an attempt had been made to compare the two types of section performed under similar conditions.

There is no doubt that throughout the country at the present time, the low-flap type of sections is considered better than the classical. I think that this is taken too much for granted. Proof is needed and this proof is lacking.

Any skillful operator doing the low-flap section as a routine will get good results. The question is, would he not get just as good results from the classical?

The teaching at the present time in most of the medical schools is that the low-flap section is the best. All young doctors graduating feel that they must do this type of section. They are not all going to be specialists. Many will be general practitioners in the country. They or any good abdominal surgeon can do a classical operation easily. But if they try to do a low-flap operation, they may get into serious trouble.

It is a good general principle of surgery that if a simple easy operation will do as well, it is a better operation than a complicated and difficult one. As I have said, I am not trying to prove the superiority of the classical operation. This would be foolish from the small number of cases presented. What I am hoping to do is to stimulate interest in this question so that others will submit statistics of the two types of sections performed under similar conditions.

In this city there is a wealth of material. If the doctors in charge of this material would all work up their statistics and present them, we might have reports on 2,000 sections performed by the two methods. Then by a comparison of results, the question of the superiority in these two types of section might be decided.

In closing, I wish to say that I think the results obtained depend more on the operator than on the type of section employed, and that it is unwise to insist that all operators should use one type only, until that type is definitely shown to give better results.

Patton, J. F.: Uterovaginal Fistula: A New Method of Reimplantation of the Ureter Into the Bladder, *J. Urology* 42: 1021, 1939.

Sixteen cases of uterovaginal fistula are presented, six of these coming under the author's personal observation during the past two years.

The importance of early investigation is stressed with application of appropriate therapeutic measures in an effort to preserve the kidney. A thorough urologic study is essential in every case of leakage of urine through the vagina, even when a vesicovaginal or urethrovaginal fistula is obvious. The type of therapy to be applied to uterovaginal fistula should be determined only after a careful study and should be directed primarily towards preservation of renal function and reestablishment of the urinary channel to approximate its normal state. Nephrectomy should be reserved for the irreparably damaged kidney or as a measure of last resort.

Dilatation should be the first procedure. In event of failure, uretero-ureteral anastomosis is the method of choice in high ureteral injuries and reimplantation into the bladder in low ureteral injuries. A new method of reimplantation of the ureter into the bladder through the intramural ureter which reproduces the normal condition, should be applicable in a definite percentage of cases.

J. P. GREENHILL.

STERILIZATION BY MEANS OF PERITONEOSCOPIC TUBAL FULGURATION

A PRELIMINARY REPORT

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THIS paper concerns itself entirely with a possible technique for sterilization by fulguration of the Fallopian tubes through a peritoneoscope. The many other aspects of the sterilization problem, legal, social, moral, and medical, have already received capable treatment elsewhere in the literature.

Since the first recorded tubal ligation for the purpose of producing sterility by a Dr. Lungren of Toledo, Ohio, in 1880, numerous methods of performing tubal occlusion have been advanced. In general all these methods seek to achieve common objectives, on the basis of which any new technique must also be judged:

1. *Certainty of Prevention of Conception.*—This, obviously, is the ultimate standard by which all methods must be evaluated. Surveys of the literature on this subject, however, reveal some failures with practically every method,^{1, 2} the Pomeroy technique apparently enjoying the best position in this respect.³ No report can be made at this time as to the certainty of the method here to be described, since only the passage of years and the accumulation of a large series of cases can give the ultimate answer.

2. *Preservation of Ovarian Function.*—Sterilization with castration can be achieved simply by radiation or oophorectomy. However, it is often undesirable to precipitate an artificial climacteric, and in this paper, sterilization is taken to mean sterilization without castration.

3. *Simplicity for the Patient.*—Women who are subjected to sterilization fall generally into two groups: A very small group for whom the operation amounts to an elective procedure, and the much larger group for whom pregnancy is contraindicated. For many of this latter group, general anesthesia and laparotomy with a prolonged convalescence are similarly contraindicated. In either group the ideal procedure would be one which could be carried out with a minimum invalidism. From the point of view of the length of required hospitalization, the generally accepted procedures fall into three principal classes: Those requiring laparotomy,² those performed vaginally,^{4, 5} and bicornuate intrauterine fulguration.^{6, 7} Laparotomy, regardless of the exact technique, remains a major intrusion into the peritoneal cavity, with the morbidity, mortality and convalescence commensurate with such procedure.^{8, 9} This also applies to the inguinal approach which is tantamount to a bilateral inguinal herniorrhaphy with the added disadvantage that considerable traction must be applied to the tubes at a time when they cannot be directly visualized.¹⁰ Vaginal sterilization by tubal ligation through the anterior or posterior cul-de-sac usually requires two to four days' strict confinement to bed, and five to seven days' hospitalization.⁵ Fulguration of the cornual openings of the tubes might conceivably become an office procedure, as claimed by Hyams,⁷ presenting a method requiring no hospitalization and minimal invalidism. This method, however, involves a violation of the uterine cavity, which should not



Fig. 1.—Sections taken through three consecutive blocks of tissue from treated tube; shown at increasing power of microscope projection. *A*, Area of normal tube. *B*, Section taken from margin of treated area, showing loss of cell outline and destruction of endosalpinx. *C*, Area of tubal scar showing loss of cell outline, fusion, and hyaline fibrosis.

be regarded too lightly. An interesting contribution to the problem of reducing the convalescence of tubal ligation is the revival by Adair and Brown¹¹ of puerperal sterilization, combining the postoperative hospitalization of the laparotomy with that of the delivery. This, however, solves the problem for only a select group of patients, and is not in itself without dangers.¹²

4. A fourth criterion which recurrently is suggested as an attribute of the ideal method of sterilization is *reversibility*. Naujoks¹³ has summarized the many operations which have been devised for reversible sterilization. Neither the methods most commonly employed nor the one here proposed are designed to be reversible.

TECHNIQUE

The procedure here presented consists of fulguration of the Fallopian tubes through the peritoneoscope, using high frequency, high voltage pulsating current. The technique of peritoneoscopy has been amply described by Ruddock,¹⁴ and in general we have followed his method. The patient is prepared as for laparotomy, and preoperative pentobarbital and morphine given. The patient is catheterized immediately before going to the operating room. Using local anesthesia, a 1 cm.

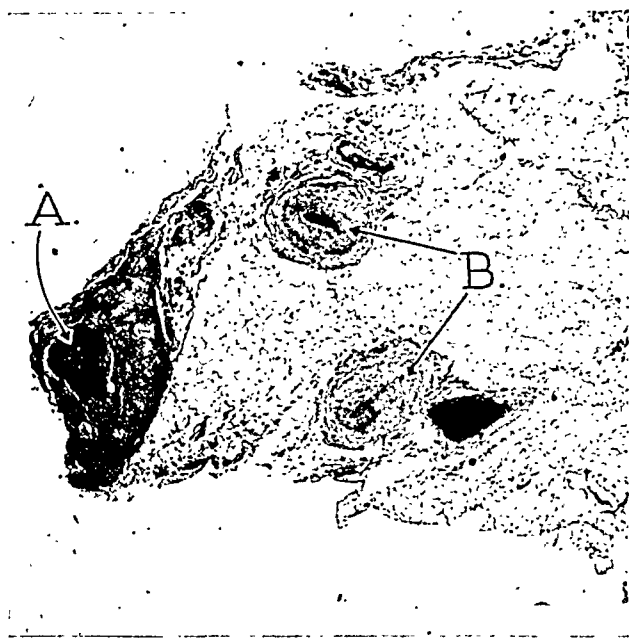


Fig. 2.—Section showing scar of treated area of dog's cornu. A, Fibrotic band of tissue. B, Local vessels (patent).

incision is made through the skin and anterior rectus sheath just below and to the left of the umbilicus. With the patient in Trendelenburg position a small trochar is inserted into the peritoneal cavity through the tiny wound, a pneumoperitoneum induced with a small rubber hand pump, and the peritoneoscope introduced into the abdominal cavity. Ordinarily one can visualize the pelvic organs satisfactorily, but should any difficulty be encountered, a hand inserted into the vagina can manipulate the uterus to bring the tubes and ovaries into view.¹⁴ Using the biopsy forceps, a Fallopian tube is grasped near the cornu and the fulgurating current applied until a segment of tube 1 cm. in length is blanched. This may be repeated in another location 3 to 5 cm. distally, and the opposite tube is then treated in a similar manner. After general abdominal inspection with the observing telescope unit of the peritoneoscope, the air is released from the abdomen, the peritoneoscope withdrawn and the wound closed with two fine silk sutures. The patient ordinarily remains in the hospital twelve to eighteen hours, and the sutures are removed in about five days.

PATHOLOGY

Six weeks following fulguration, gross examination showed marked fibrosis of the tubes which were contracted to the caliber of a fine cord over a distance of 1 or 2 cm. at each point of treatment. There were a few small adhesions involving one of the fulgurated segments. Cannulization of the normal untreated sections of the tubes revealed the patency of these areas (Fig. 1, *A*). That no fistulas were present was demonstrated by the injection of fluid into the tubes from both the uterine and fimbriated ends.

Microscopic examination revealed destruction of the endosalpinx with marked hyaline fibrosis of the entire tube in that area (Fig. 1, *B* and *C*). Patency of the ovarian vessels was demonstrated to have been preserved. Animal material also removed six weeks following fulguration of the same type but slightly more prolonged, showed reduction of the dog's cornu to thin threads of tissue over the



Fig. 3.—Untreated section of dog's cornu.

areas treated. Microscopic examination of sections taken through several of these areas failed to demonstrate any trace of the uterine structure. The fine thread visible upon gross inspection was found to be composed of the uterine vessels and a contracted strand of fibrous scar (Fig. 2). The untreated segments of the cornu demonstrated continued vitality of the endometrium and normal appearance of the cornual wall (Fig. 3).

COMMENT

Cauterization of the Fallopian tubes to produce their occlusion was suggested as early as 1848 by Froriep,¹⁵ who proposed that fused silver nitrate be guided to the uterine horns by hollow conductors. Prudnikoff,¹⁶ in 1912, suggested transuterine coagulation of the cornual stomas as a means of producing sterility. Cauterization or fulguration so employed, however, has the disadvantage that the application is carried out without direct visualization.

Peritoneoscopic fulguration of the Fallopian tubes for the purpose of producing sterilization, has not, to our knowledge, ever before been tried. We do not believe that the literature contains any suggestion concerning this use of the peritoneoscope. We believe that this method warrants further study and clinical trial, because it appears to present certain advantages over various other generally accepted procedures:

Safety.—Ruddock¹⁴ reports accidental perforation of an abdominal viscus in 8 (0.88 per cent) of his 900 cases recently surveyed. All but one of these accidents were attributable to abdominal pathology suspected prior to peritoneoscopy, and which would contraindicate any attempt at peritoneoscopic sterilization. In each case laparotomy allowed prompt repair of the damage and the morbidity was no greater than for simple laparotomy. He reports one death from delayed hemorrhage from liver biopsy, which would not occur with simple fulguration of the Fallopian tubes. In the 175 peritoneoscopic examinations done at the University Hospital in the past three years, a huge liver extending below the umbilicus was perforated, and the colon, adherent to an old scar in the anterior abdominal wall, was entered. Immediate repair was accomplished and recovery was uneventful in both instances. Since the procedure is performed under local anesthesia and with very minimal tissue damage, the dangers inherent in the use of general anesthesia and the likelihood of postoperative embolism, atelectasis and pneumonia are eliminated. The danger of postoperative hernia is nil. In those cases where laparotomy has followed peritoneoscopy, adhesions to previously cauterized areas has not been a prominent feature. We see no reason to believe that adhesions resulting from this procedure should be any more serious than those which form around the nonabsorbable tubal ligature of the Madlener operation.

Economy.—Although the procedure is usually performed in an operating room equipped with instruments readily available for prompt laparotomy in event of accident, the expense is considerably reduced through the elimination of charges for general anesthesia, assistants, and prolonged period of hospitalization.

Effectiveness.—While, as discussed above, the ultimate test of effectiveness of a sterilization method must rest with the accumulation of a large series of cases, observed for several years, the effectiveness of this method to produce tubal occlusion cannot be doubted. Only after further study and clinical application can we evaluate the place of this procedure in the field of sterilization.

CONCLUSIONS

1. A possible method of sterilization is presented, based on the production of Fallopian tubal occlusion by multiple local fulgurations through a peritoneoscope.

2. Pathologic material from both human and animal subjects is presented to demonstrate the effectiveness of the method in the production of tubal occlusion.

3. By such a method of sterilization, morbidity, length of convalescence, and total expense can be reduced to a minimum.

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STUDIES IN PELVIC IONTOPHORESIS OF A CHOLINE COMPOUND*

II. PREOPERATIVE MANAGEMENT OF UTERINE MYOMAS COMPLICATED BY PELVIC INFECTION, WITH A REPORT OF 39 CASES

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MYOMAS of the uterus are frequently associated with inflammatory disease of the tubes and ovaries.

Kelly and Cullen,¹ in 934 cases, found one or both tubes adherent to the tumor in 423. The frequency in negroes was nearly twice that in white women. The incidence of association in colored women is reported by Miller² in 150 cases as 93 per cent, by Alsobrook³ in 1,000 cases as 99.1 per cent, and by Witherspoon and Butler⁴ in 125 cases as 100 per cent.

Keene and Kimbrough,⁵ however, found inflammatory lesions in 23.3 per cent of their cases, and Baer and his associates⁶ found tubal pathology in only 13.3 per cent of 938 cases. These authors do not indicate the ratio of colored to white women in their cases. Schmitz,⁷ reporting the mortality of 3,129 supravaginal hysterectomies performed for myomas at the Cook County Hospital, where about half of the patients are negroes, found that pelvic inflammatory disease complicated 38 per cent of their cases, and showed that it contributed heavily to the mortality. In this large series, there were 78 deaths, a mortality of but 2.1 per cent, yet in 85 per cent of the deaths, or 68 cases, the myomas were associated with pelvic inflammatory disease. Greenhill,⁸ in the same type of cases, found that the mortality was ten times as great as for simple supravaginal hysterectomy. There is good evidence for marked increase in morbidity as well.^{7, 9}

Removal of the inflamed adnexa, distorted and often adherent to the pelvic walls and intestines as well as the uterus, with collections of pus within or about them, adds greatly to the risk of operation by increasing the difficulty of pelvic surgery and by provoking dangerous peritonitis. Infrequently these lesions are caused by spread of infection from the tumor itself, but generally infection comes from without, either specific in origin or following abortion or parturition.

*Read at a meeting of the Brooklyn Gynecological Society, February 7, 1941.

Women with myomas admitted to the hospital with a history of pelvic pain, elevated temperature, leucocytosis, and accelerated sedimentation time are not good risks for operation. Adnexal pathology may be suspected, yet diagnosis may not be easy when myomas fill the pelvic cavity, and occasionally conditions within the tumor itself, such as degeneration, may account for the same clinical picture.

It has been our experience that strict insistence upon a sedimentation time of eighty minutes is an excellent criterion of relative safety. Slight leucocytosis may be disregarded, but operation should be deferred until the temperature and sedimentation time are satisfactory. It is our experience that normal sedimentation is re-established very slowly, however, when disturbed by degenerative processes within the tumor, and contraindication to operation is not present as in adnexal disease. The period of preoperative observation may be shortened if the nature of the complication is known.

In the course of our studies in iontophoresis of a choline compound, we have reported our results in the treatment of pelvic infections¹⁰ and have fully described the rationale and technique of the therapy. Systemic reactions have also been reported. Our results in tuboovarian infections have been sufficiently good to warrant continued use of this method of treatment when operation and other methods of therapy are not indicated.

CASE MATERIAL

During the past two and one-half years, 39 women with myomas and clinical evidence of pelvic inflammatory disease, or tumor degeneration or both, were given iontophoresis therapy; 37 cases are from the Kings County Hospital, and 2 cases from the Long Island College Hospital.*

All but 5 were negroes; 22 were multiparas, and 17 primiparas, 7 of whom gave a history of abortion. The ages ranged from 35 to 50 years in 21 cases, from 25 to 34 years in 13 cases, and from 18 to 24 years in 5 cases.

In 32 cases abdominal tenderness or peritoneal rebound pain was noted, and in 27 cases a firm mass could be felt in the abdomen. In 18 cases the mass was larger than a five months' pregnancy, and in 9 cases the size of the mass approximated a pregnancy of three to five months' duration. Pain was a prominent symptom in 32 cases. In 12 cases there was a clear history of previous specific infection, and 4 women had suffered complications following induced abortion. Tender adnexal masses were present in 25 cases.

The temperature was above normal in 25 cases, generally between 100° and 102° F. Anemia was uncommon; in only 8 cases was the hemoglobin below 70 per cent Sahli, and in each of these it was at least 60 per cent. In spite of evidence of pelvic infection in 32 cases, leucocyte counts were generally low, above 10,000 and not higher than 15,000 in only 13 cases, though the count was 23,300 in one case. The polymorphonuclear differential count followed the total leucocyte count in its variation.

Sedimentation time was a much better index of the presence and activity of infection. In all but two cases it was accelerated. The normal figure according to the method we use is eighty minutes plus for a drop of 18 mm. of the erythrocyte mass in the sedimentation time tube. The time noted on admission to the hospital is shown in Table I.

In 28 cases the diagnosis of adnexal disease associated with uterine myomas was made, yet in 4 of these cases unsuspected degeneration of a fibroid was present as well, in 1 case proving to be the sole complication. In 8 cases the differential diagnosis could not be made. At operation, degeneration alone was found in 1 case, pelvic infection alone in 4 cases, and both degeneration and infection in 3 cases.

*We are indebted to Dr. William A. Jewett and Dr. Harvey B. Matthews for permission to use these cases.

TABLE I

DATE	CHICAGO MUNICIPAL SOCIAL HYGIENE CLINIC		Hb	CHICAGO LYING-IN HOSPITAL				TREATMENT
	SMEAR	CULTURE		SMEAR		CULTURE		
				URETHRA	CERVIX	CERVIX	URETHRA	
				PUS CELLS	PUS CELLS	CERVIX	URETHRA	
12/ 5/39	-			- Many	- Epith.	4+	-	Local
12/12/39	-			- Many	- Many	-	-	
1/10/40	-			- Many	- Shreds	-	-	
1/25/40	-			- Mod.	- Epith.	-	-	
Postmenstr.								
2/20/40	-			- Mod.	- Epith.	-	-	
2/28/40	-			- Many	- Few	-	-	
Menses								
3/19/40	-			- Rare	- Mod.	4+	4+	
4/ 2/40	-			- Few	- Epith.	-	-	
4/15/40	-			- Few	- Epith.	-	-	

TABLE II

DATE	CHICAGO MUNICIPAL SOCIAL HYGIENE CLINIC		Hb	CHICAGO LYING-IN HOSPITAL				TREATMENT
	SMEAR	CULTURE		SMEAR		CULTURE		
				CERVIX	URETHRA	CERVIX	URETHRA	
2/6/40	-			? Diplo-coccus	- Occa-sional	4+	4+	Local
2/15	-			- Occa-sional	- Shreds	4+	-	
2/20	-			- Few	- Shreds	-	-	
2/27	-			- Few	- Shreds	-	-	
Postmenstr.								
3/5	-			- Few	- Few	Overgrown		
3/18	-			- Epith.	- Shreds	-	-	
Menses								
3/29	-			- Epith.		-	-	
Postmenstr.								
4/5	-			- Mod.	- Epith.	+	+	
4/12	-			- Mod.	- Epith.	-	-	
4/19	-			- Many	- Shreds	-	-	

These patients might have been considered cured even in a clinic which required several consecutive negative smears for discharge. Table IV might explain some of the reported relapses in patients who had received chemotherapy but whose negative smears were not an indication of cure. Table V shows twelve patients whose cultures remained positive for more than two weeks after smears had become negative.

Notwithstanding the fact that cultures have been transported for several miles during all seasons and without special precautions for protection, they have proved to be far superior to smears as a criterion of cure. In women the status of infection is determined by smears and

Other patients showed persistent positive cultures although the smears were consistently negative.

Supravaginal hysterectomy with removal of both tubes and ovaries was performed on September 20. The uterus was as large as a six months' pregnancy and studded with fibroids, with thickened tubes adherent posteriorly. Many tumors were in varying stages of red degeneration and liquefaction necrosis. Histologic examination of the tubes and ovaries showed adhesions, edema, and fusion of contiguous folds in the tubal lumina. No inflammatory cells or exudate were seen, and it is possible that hyperemia and edema were due to treatment. Postoperative course was febrile, the temperature reaching 101° F. She was discharged well on the thirteenth day after operation.

In our experience, myomas with degeneration have responded unfavorably to iontophoresis, and we have made use of this finding in arriving at a diagnosis (Table II).

TABLE II. EFFECT OF IONTOPHORESIS ON SEDIMENTATION TIME. DEGENERATION OF MYOMAS

TYPE OF DEGENERATION	NO. OF TREATMENTS	TIME PERIOD (DAYS)	CHANGE IN SEDIMENTATION TIME (MINUTES)
Red, extensive	4	10	20 unchanged
Red and liquefaction	7	28	40 to 22
Liquefaction	9	28	45 to 20
Liquefaction	4	42	20 to 15

TABLE III. EFFECT OF IONTOPHORESIS ON SEDIMENTATION TIME. MYOMAS ASSOCIATED WITH PELVIC INFLAMMATION

ADNEXAL PATHOLOGY (LABORATORY)	NO. OF TREATMENTS	DAYS	CHANGE IN SEDIMENTATION TIME (MINUTES)
Pyosalpinx; chronic salpingitis	4	8	20 to 80
Edema of tubes	8	20	27 to 80
Acute and chronic salpingitis	9	25	21 to 80
Healed salpingitis and perisalpingitis	4	10	20 to 80
Subacute and chronic salpingitis; abscess	6	17	35 to 80
Subacute and chronic salpingitis; pyosalinx	5	10	35 to 80
Subacute salpingitis	5	14	40 to 80
Peri-oophoritis	7	14	20 to 75
Subacute and chronic salpingitis	6	16	40 to 76
Subsiding adnexal infection	3	5	60 to 80
Subacute and chronic salpingitis; large cyst	8	25	12 to 22

Women with pelvic inflammation and myomas not undergoing degenerative changes responded very well to iontophoresis as a rule. Pain was relieved in 75 per cent of the cases. Sedimentation time response is noted in 12 cases in Table III. All these patients were operated upon, and all uteri, tubes, and ovaries were examined microscopically.

An example of the type of response seen in this group follows:

E. S., colored, aged 45 years, was a patient in Kings County Hospital for two weeks in June and July, 1937, with a diagnosis of myoma of the uterus complicated by pelvic inflammatory disease. After a febrile course with temperature reaching 103° F., she signed her release.

She was readmitted on April 11, 1939, with a temperature of 100.4° F., complaining of lower abdominal pain. Examination showed tenderness in both lower

TABLE I. SEDIMENTATION TIME ON ADMISSION

TIME	NO. OF CASES
7 to 20 minutes	12
20 to 40 minutes	14
40 to 60 minutes	11
60 to 80 minutes	2
Total	39

In only 2 cases was the clinical evidence definite enough to warrant a diagnosis of degeneration alone, and this was confirmed at operation. In 1 case, in which the sedimentation rate was forty minutes, no cause was found at operation.

Hysterectomy was performed in 32 cases, with removal of one or both adnexa in 27 cases. The high percentage of operation afforded an excellent opportunity for ascertaining the type of pathology treated. In every case the possible effect of iontophoresis was carefully studied, and all excised tissue subjected to gross and microscopic examination.

In 11 cases myomas in varying stages of red degeneration and liquefaction necrosis were found, and in 4 of these cases no evidence of pelvic inflammation could be demonstrated. Edema and congestion were occasionally observed. In the adnexal inflammation group, there were 5 cases of pyosalpinx or ovarian abscess.

In 12 cases marked edema and congestion were observed on histologic examination of the tubes, and hyperemia of the pelvic peritoneum and occasionally petechial hemorrhages of the serosa of the uterus were noted at operation. Recent experiments in which iontophoresis had been given a few hours prior to laparotomy for pelvic pathology not associated with infection indicate that these findings can be duplicated.

At first it was thought best to allow a reasonable time for the usual bed rest improvement, before instituting iontophoresis. So, in 7 cases, at least two weeks elapsed before special treatment. Later, when we thought iontophoresis valuable in shortening preoperative preparation, it was given earlier, though in 9 cases, five days at least elapsed. An average of six treatments was given, one every other day. Twelve was the largest number of treatments given to one patient.

Operation was performed when the clinical objectives of normal temperature over a period of time, normal leucocyte count with normal polymorphonuclear differential and normal sedimentation time were achieved. If temperature remained normal over a period of one or two weeks, yet sedimentation time failed to reach normal, laparotomy was performed in spite of this finding, for we assumed that degenerated myomas rather than pelvic infection would be found. Brief history of the following two cases will illustrate:

CASE 1.—M. D., colored, aged 34 years, was admitted to Kings County Hospital on Jan. 29, 1939, with a history of vaginal spotting and right lower quadrant pain for one week. Temperature was 101° F., leucocyte count 12,400, hemoglobin 73 per cent Sahli, and sedimentation time twenty minutes. A hard smooth tender mass rising to the umbilicus was felt in the abdomen. The impression was degeneration of a myoma.

Temperature became normal two days later and remained so. Iontophoresis was begun on February 10, and four treatments were given during the next ten days. Sedimentation time remained twenty minutes. Supravaginal hysterectomy was performed on February 27. At operation, no pelvic inflammatory disease was seen; two huge fibroids were found, the larger showing extensive red degeneration. Post-operative recovery was smooth.

CASE 2.—E. L., colored, aged 39 years, was admitted to Kings County Hospital on July 27, 1939, with a history of progressive enlargement of the abdomen for ten months and discomfort in the abdomen for three months. Examination showed a large, tender, multinodular mass fixed in the lower abdomen. The leucocyte count was 7,600 with 54 per cent polymorphonuclears, 74 per cent Sahli hemoglobin, and sedimentation time sixty minutes. She remained afebrile for three weeks, but the sedimentation time became forty minutes. Iontophoresis was begun on August 23, and 7 treatments were given during the next nineteen days.

TABLE IV. EFFECT OF IONTOPHORESIS ON SEDIMENTATION TIME. DEGENERATION OF MYOMAS AND PELVIC INFLAMMATION

TYPE (LABORATORY)	INFECTION (LABORATORY)	NO. OF TREAT- MENTS	DAYS	CHANGE IN SEDIMENTA- TION TIME (MINUTES)
Red and liquefaction	Perisalpingo-oophoritis; hydrosalpinx	5	11	30 to 80
Red, subsiding	Perisalpingo-oophoritis	1	9	30 to 80
Red, subsiding	Subacute and chronic salpingitis	6	30	23 to 70
Hemorrhage and edema	Subacute and chronic salpingitis	3	4	25 to 75
All types	Bilateral pyosalpinx; abscess	12	30	10 to 35
Hemorrhage and edema	Perisalpingitis; hydro- salpinx	3	11	45 to 15

MORTALITY

Death in one case, clearly not due to iontophoresis therapy, is reported:

W. L., colored, aged 43 years, was admitted to Kings County Hospital on July 8, 1939, complaining of abdominal pain. The uterus was nodular and the size of a three and one-half months' pregnancy; motion caused pain. A tender adnexal mass was palpated. Sedimentation time was twenty minutes.

Iontophoresis therapy was begun on August 12 because of persistence of rapid sedimentation time. Five treatments were given before September 1, with a rise in sedimentation time to fifty minutes.

Supravaginal hysterectomy with bilateral salpingo-oophorectomy was performed on September 26. At operation the uterus was enlarged to the size of a three months' pregnancy by myomas, and both adnexa were involved in bilateral chronic inflammatory masses which were adherent to the posterior surface of the uterus and to the peritoneum of the cul-de-sac. During the course of the operation, a large hematoma formed in the right broad ligament.

The pathologic report described myomas of the uterus and diffuse subacute and chronic salpingitis with perisalpingitis and peri-oophoritis.

On the day following operation when the patient appeared to be in good condition, she suddenly went into collapse, showed muscular twitchings of the face, and died. Death was thought to be due to postoperative embolism.

EVALUATION OF IONTOPHORESIS THERAPY

Our estimation of the value of pelvic iontophoresis is based upon unusually rapid improvement in the clinical and laboratory data significant of infection. Subsidence of fever, pain and abdominal tenderness, diminution in size of inflammatory masses, and more favorable leucocyte counts and sedimentation rates have been the criteria of improvement.

It is clear of course, that subacute or chronic pelvic inflammatory disease, whether associated with myomas of the uterus or not, tends to improve on bed rest alone.

In our opinion it is impossible to set up a parallel series in study of the effect of any method of therapy in pelvic inflammatory disease. Adnexal pathology varies so widely that lesions apparently similar are not identical in histology, bacteriology, or type, character and location of associated pelvic exudates. Observation of approximately 500 cases

quadrants of the abdomen, the uterus enlarged to the size of a two and one-half months' pregnancy, and a tender adnexal mass posterior to the uterus. The leucocyte count was 6,000 with 71 per cent polymorphonuclears, hemoglobin 74 per cent, and the sedimentation time twenty minutes.

Pelvic iontophoresis was given four times between April 14 and April 20. The sedimentation time on April 19 was more than eighty minutes.

Supravaginal hysterectomy, with bilateral salpingo-oophorectomy, was performed on April 24. The uterus was enlarged by myomas to the size of a two and one-half months' pregnancy, and both tubes and ovaries were densely adherent in the cul-de-sac. One tube was the site of a pyosalpinx, the other tube showing evidence of chronic salpingitis. On histologic examination, edema and marked dilatation of blood vessels were seen. Postoperative recovery was smooth. (Fig. 1.)

When degenerating myomas were associated with pelvic inflammatory disease, a variety of results were obtained as shown in Table IV.

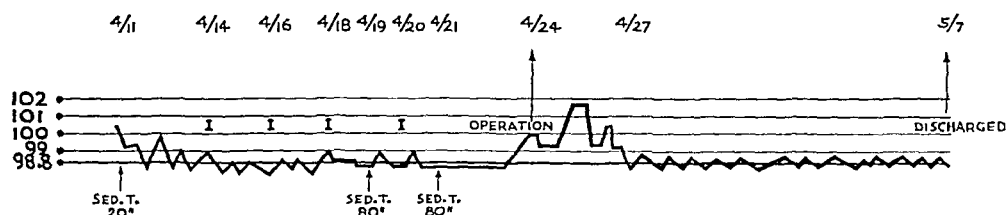


Fig. 1.—E. S. Fibroid uterus with pyosalpinx. Supravaginal hysterectomy and bilateral salpingo-oophorectomy. Smooth postoperative course. Sed. T., sedimentation time; I, iontophoresis.

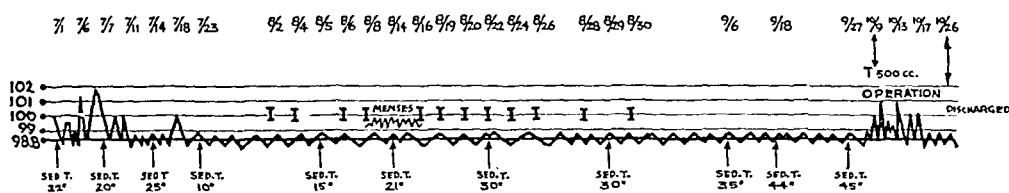


Fig. 2.—M. W. Multinodular fibroid uterus with degeneration and massive pelvic and abdominal infection. (Bilateral pyosalpinx, ovarian abscess, and generalized peritoneal adhesions.) Sed. T., sedimentation time; I, iontophoresis; T, transfusion.

One of these cases is briefly reported since, after a control period in the hospital of one month, with sedimentation time becoming more rapid; improvement coincided with iontophoresis therapy. Her progress is shown in Fig. 2.

M. W., colored, aged 29 years, was admitted to Kings County Hospital on July 1, 1939, complaining of abdominal pain and vaginal bleeding for fifteen days. Examination showed a huge multinodular mass filling the pelvis and rising 7 cm. above the umbilicus. X-ray showed elevation and flattening of the dome of the diaphragm. Temperature was 99.6° F., leucocyte count 23,300 with 78 per cent polymorphonuclears, hemoglobin 71 per cent Sahli, and sedimentation time twenty-two minutes.

After bed rest for one month, sedimentation time was ten minutes, temperature rising occasionally to 101.8° F. Iontophoresis was given eight times between August 2 and August 30. Sedimentation time rose to forty-four minutes on September 18, and forty-five minutes one week later.

On October 9 supravaginal hysterectomy with removal of both adnexa was performed. The tumor was adherent to sigmoid, transverse colon, and stomach; two large pyosalpinges were present. Peritoneal adhesions were fibrinous, separating easily, with small pockets of clear serous fluid between them. Postoperative recovery was smooth. (Fig. 2.)

The pathologic report showed myomas in various stages of degeneration, including edema, red degeneration, and calcification; the adnexa showed bilateral pyosalpinx and ovarian abscess.

6. In cases of myomas, where the differential diagnosis between accompanying infection and degeneration is difficult, iontophoresis may be helpful in preventing undue preoperative delay while awaiting satisfactory laboratory data.

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DISCUSSION

DR. MORRIS GLASS.—From Jan. 1, 1935, to Dec. 31, 1940, 610 uteri have been removed by the College Division at the Kings County Hospital; 49 vaginally and the remaining 561 through the abdomen. The abdominal hysterectomies were divided as follows: 473 supravaginal operations; 5 patients died, yielding a mortality of a little more than 1 per cent. The remaining 88 were total hysterectomies, and in this group 4 patients, or 4.5 per cent, died. In analyzing the 9 deaths it was noted that 6, or 66⅔ per cent, were associated with fibroids having pelvic inflammation. In addition, 4 of the patients eviscerated postoperatively, which undoubtedly was a major factor in causing death.

Two procedures have been instituted recently in the hope of decreasing our mortality. The first of these was pelvic iontophoresis. For the past two and one-half years, this form of treatment has been used, as mentioned tonight, on patients with fibroids complicated by inflammatory adnexal masses. It would appear from the results that the preoperative stay in the hospital might be shortened, the masses tend to become smaller, less tender and more mobile and the cellulitic involvement less pronounced. All of these factors would tend to decrease the difficulties at operation and lead to a smoother and less complicated postoperative course. It is plausible to presuppose, however, that pelvic iontophoresis would have no effect whatsoever on large fibroids in which extensive degeneration had taken place, because of the marked disturbance of the blood supply in the tumor.

The second important addition to our armamentarium in reducing the mortality, we feel, is the decrease of wound disruption as a postoperative complication. Since November, 1939, all laparotomies, unless a specific contraindication existed, have been sutured throughout with interrupted fine black silk, including the peritoneum. During this period there has been no evisceration on our service. We feel that the elimination of this formidable complication has helped us improve our end-results attested by our hysterectomy figures for the year 1940, during which time 88 supravaginal and 33 total hysterectomies were performed without mortality.

Guimaraes, P. Duarte. A Case of Intra-peritoneal Hemorrhage of Ovarian Origin, Rev. de gynec. e d'obst. (Rio de Janeiro) 2: 20, 1940.

The author reports the history of a girl 17 years old with a clinical history of recurrent appendicitis. At operation, the ovary on the right side was found to be ruptured and bleeding; the abdominal cavity was full of blood. The ovary was not removed, but the rent in it was sutured. The patient recovered. The author discusses at great length the differential diagnosis between appendicitis, follicular hemorrhage, ectopic pregnancy, etc.

MARIO A. CASTALLO.

of pelvic infection a year in our wards at Kings County Hospital has made us reasonably familiar with what to expect from bed rest, transfusion, and supportive therapy. Not infrequently rapid sedimentation time is the only indication of complication. On the basis of objective findings alone, we have classified our results in all 39 cases.

1. Good effect: When response has been striking.
2. Doubtful effect: When response has been good, but no better than we have seen occur with ordinary supportive therapy.
3. No effect: When the condition remained essentially unchanged.
4. Untoward effect: When clinical evidence of exacerbation of infection or degeneration followed therapy.

TABLE V. EFFECT OF IONTOPHORESIS IN MYOMAS OF THE UTERUS

EFFECT	PELVIC INFLAMMATION	DEGENERATION	COMBINED
Good	11	—	4
Doubtful	7	—	2
Untoward	2	3	1
None	5	1	—

In 3 cases with questionable complication, 2 had a good and one had a doubtful result.

The best results were obtained in cases of myomas associated with pelvic inflammatory disease. No result at all or exacerbation of symptoms followed use of iontophoresis in cases of myomas with degeneration.

We believe that iontophoresis is a valuable method of therapy for chronic pelvic inflammatory disease associated with uterine myomas. The preoperative time is shortened and the risk of operation decreased. Our experience with iontophoresis in degenerated myomas is limited, yet it may be a new aid in diagnosis of difficult cases.

SUMMARY AND CONCLUSIONS

1. We have called attention to the risk of operation when myomas are associated with pelvic inflammation.
2. Pelvic iontophoresis was given during the preoperative preparation of 39 cases of myomas of the uterus, associated with pelvic inflammatory disease, degeneration of myomas, or both. Hysterectomy was performed in 32 cases, and in 27 one or both tubes and ovaries were excised.
3. Material for pathologic study was available, thus affording an excellent opportunity for determining the type of pathology treated and the effects produced.
4. The preoperative preparation of myomas associated with pelvic inflammatory disease may frequently be shortened by this method of therapy, and the operative risk decreased.
5. In cases of myomas complicated by degeneration, iontophoresis either had no effect, or accentuated the degenerative processes.

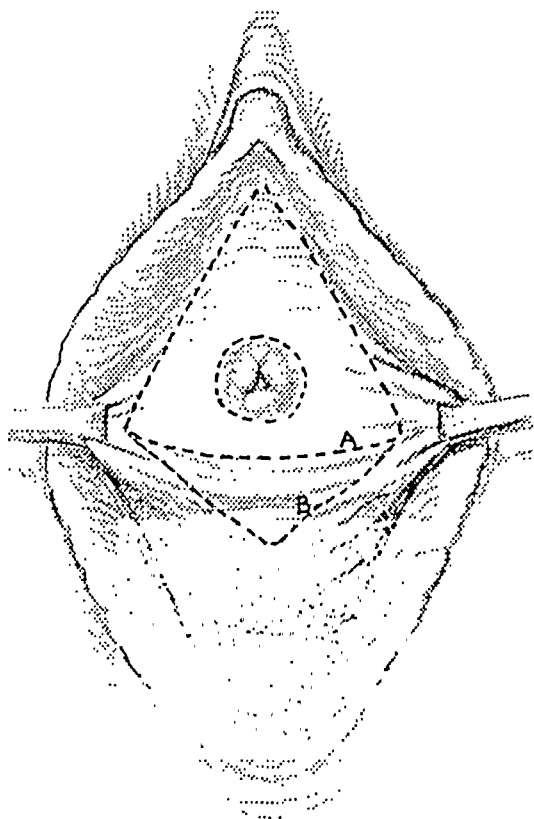


Fig. 1.—Incisions in the vestibular and vaginal mucosa. These sketches depict a secondary operation for incontinence, in which a previous operation cured an associated cystocele without establishing bladder control. *A* shows the lower part of the incision in this case. *B* shows the lower part of the incision as usually made.

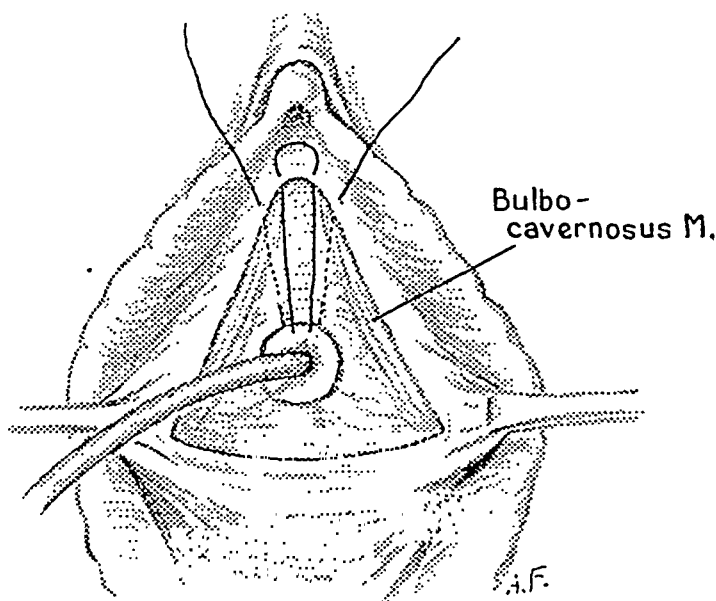


Fig. 2.—Retention catheter in place. Vestibule and adjacent vagina denuded, except for one-eighth inch of mucosa left around the meatus. A Bonney (fixation, or "W") suture replaces the anterior traction suture. Urinary meatus is brought up under the clitoris. This suture is not tied at this time.

PARAURETHRAL FIXATION

A NEW OPERATION FOR THE CURE OF RELATIVE INCONTINENCE OF URINE IN WOMEN

SAMUEL GORDON BERKOW, M.D., PERTH AMBOY, N. J.

PARAURETHRAL fixation" is a modified combination of two procedures long used for the relief of urinary incontinence in women. These procedures are: (1) advancement of the urinary meatus to just below the clitoris, as recommended by Pawlik, Dudley and others, and (2) suburethral reefing.

Reports on either type of operation alone claim numerous successes and admit some failures. But my personal experience, limited to suburethral imbrication and the Kelly stitch, has been disappointing. Recent literature indicates that the "few failures" comprise from 15 per cent to 40 per cent.

The first step of the operation proposed elevates the lax urethra, increasing its length and narrowing its lumen; the second step buttresses the lengthened urethra with two layers of muscle, the pubococcygeal fibers of the levators* forming the first layer, and the bulbocavernosus muscles the second layer.

The primary object of this operation is not merely to fuse two techniques. The satisfactory results of parametrial fixation in uterine prolapse prompted the application of similar principles to the surgery of incontinence. More directly, therefore, the new operation is derived from the technique of parametrial fixation, as described by Dr. Robert T. Frank. For this reason, the name paraurethral fixation, suggested by Dr. M. A. Goldberger, has been adopted for this operation.

In the past five years, 21 patients have been operated upon by me with this technique. All of these patients had relative or "stress" incontinence. Two patients were operated upon within the past month, and although they are now continent, a longer time must elapse before the results can be properly evaluated. The first patient and one other were not relieved. In the remaining 17 patients complete bladder control was restored. When these patients were last seen, two months to nearly three years after operation, incontinence had not recurred in a single instance.

TECHNIQUE

After due preparation, with the patient in the lithotomy position, each labium is fastened laterally with a suture. A traction suture is placed just below the clitoris, and another is placed carefully in the vaginal mucosa below the urethral opening of the bladder. This point need not be defined exactly. Sufficient exposure will be obtained if this suture is placed about 5 cm. below the external urinary meatus. The traction sutures are not tied. Upward traction on the superior suture and down-

*Variously named in gynecologic literature (pubocervical muscles, fascia pubocervicalis, pubovesicocervical musculofascial sheath), these structures are anatomically the median fibers of the pubococcygeus muscles, part of the levator sling.

ward and outward traction on the inferior suture brings the quadrilateral area of the vestibule and anterior vagina into a single plane. Keeping the whole area under sufficient tension, the quadrangle is outlined by a mucosal incision. This starts below the clitoris, runs parallel to the retracted labia minora and then downward and medially to the vaginal mucosa just above the lower suture. A second incision encircles the urinary meatus about one-eighth inch from the orifice. By sharp and blunt dissection, the area delimited by these incisions is denuded of its mucosa (Fig. 1). A self-retaining catheter inserted into the bladder aids the suburethral denudation.

Now a Bonney ("W") suture in the upper angle of this incision replaces the superior traction suture. Twisted silk has been used in this suture, but chromicized catgut (No. 2) has proved equally satisfactory. This suture is best started through the apex of the incision, passing through the mucous membrane close to the cut edge.



Fig. 5.—Operation completed. Catheter removed. (It is better to leave it in for forty-eight hours.)

Each end of this suture, threaded on a curved cutting needle, is brought down to the urinary meatus, and is carried deeply upward and laterally through the bulbocavernosus muscle on its own side, to emerge on the vestibular surface about one-fourth inch from the median line and as far in from the cut surface as possible (about one-half inch). The free ends of this suture are caught in a single clamp.

The mucosa surrounding the meatus is now grasped with a dissection forceps. By traction on the suture and the forceps, the urethra is brought up under the clitoris, until the cut mucosal surfaces are opposed. If the urethra cannot be elevated readily, it is necessary to free the urethra with the back of the scalpel by gentle pressure against the lateral attachments of the urethra. An assistant holds the urethra in the new position by continued traction on the clamp holding the free ends of the W suture.

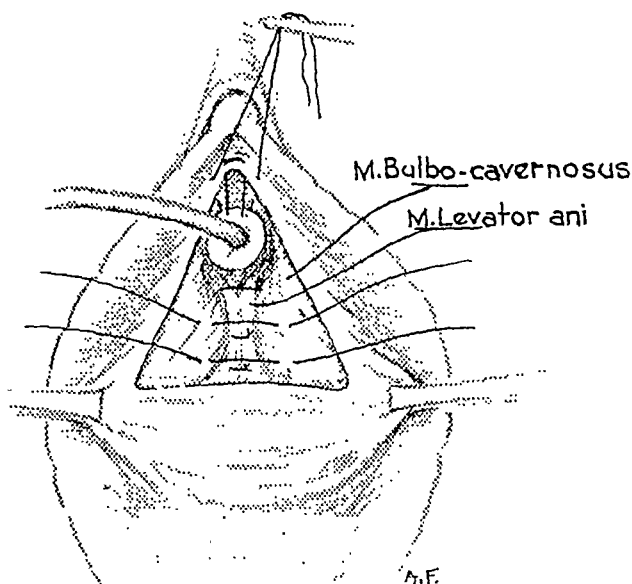


Fig. 3.—Urethra pulled up (for purposes of illustration, the mucosal rim around the meatus has not been pulled up to the mucosa below the clitoris). First row of reefing sutures, bringing the pubococcygeal fibers of the levators together under the urethra. The highest of these sutures should be at, or just behind, the inferior margin of the symphysis. Second row of reefing sutures in place, not tied.

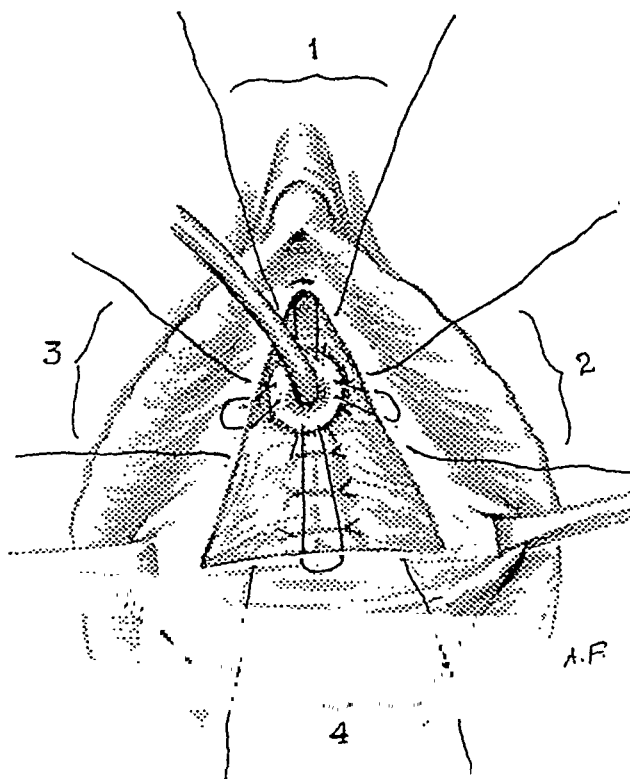


Fig. 4.—Second row of reefing (or buttressing) sutures tied, bringing the bulbo-cavernosus muscles together under the urethra. These sutures cover the sutured pubococcygeus and extend up on the anterior surface of the symphysis to the meatus. The paraurethral fixation sutures are inserted as numbered, and tied in the following order: 2, 3, 4, 1.

cultures from both cervix and urethra. Since one or both sites may be involved, Table VI presents the results of both cervical and urethral smears as compared with cultures.

The smears have been examined very carefully. Even after long search there are many slides in which typical diplococci can be found extracellularly but not intracellularly. These slides have been further subdivided into those in which the diplococci were found in typical clump formation and those in which only scattered unclumped organisms were found.

TABLE III

DATE	CHICAGO MUNICIPAL SOCIAL HYGIENE CLINIC		Hb	CHICAGO LYING-IN HOSPITAL						TREATMENT AND PROGRESS NOTES	
	SMEAR	CULTURE		SMEAR		CULTURE		DRUG AND DOSAGE			
				CERVIX	URETHRA	CERVIX	URETHRA				
				PUS CELLS	PUS CELLS	CERVIX	URETHRA				
10/23/39	+									Routine examination. No symptoms	
10/30/39	+		65%	+	Many	-	Mod.	4+	4+	Local	Asymptomatic
11/13/39	-			-	Many	-	Few	4+	4+		Asymptomatic
11/16/39	-			-	Occ.	-	Epith.	4+	4+		Feels well
11/20/39	-			E†	Many	-	Epith.	4+	4+		Asymptomatic
11/27/39	-			-	L. bac	-	Mod.	4+	og*		
12/ 4/39	-			E†	Many	-	Few	4+	-		Feels well
12/ 7/39	-			-	Few	-	Many	2+	-		Profuse mucoid cervical discharge
12/11/39				-	Mod.	-	Few	3+	-		Discharge. Denies contact
12/14/39	-										
12/18/39	-			-	Few	-	Epith.	-	-		Discharge decreased
12/26/39	-										
1/ 8/40	-			-	Many	-	Epith.	2+	-		No complaints. Discharge decreasing
1/15/40	-			-	Many	-	Epith.	-	-		Asymptomatic
1/22/40	-			-	L. bac	-	Epith.	2+	-		Profuse vaginal discharge
2/ 5/40	-			-	Mod.	-	Epith.	4+	-		Denies contact. Moderate discharge
2/ 7/40											
3/ 4/40	-			-	Mod.	-	Epith.	-	og*		Discharge. Denies contact
3/11/40	-			E	Mod.	E	Epith.	og*	og*		Asymptomatic. Moderate discharge
3/18/40	-			-	Many	-	Epith.	4+	4+		Urethra slightly inflamed. Cervical discharge
4/ 1/40	-			-	Few	-	Epith.	-	-		Profuse discharge
4/15/40	-			-	Mod.	-	Epith.	4+	4+		Purulent discharge. Denies contact

*Overgrowth.

†Typical extracellular diplococci in clumps.

‡Lactobacillus,

Starting below the urethrovesicle junction, which is located by gentle traction on the catheter, interrupted sutures of chromicized catgut are placed in the fascia-covered levator muscle (pubococcygeal portion) to either side of the urethra. The last suture is placed below the meatus. These sutures are tied from below upward, buttressing the posterior surface of the urethra with the musculofascial layer of suburethral tissue. The medial borders of the bulbocavernosus muscles now stand out sharply on either side of the upper half of the first row of reefing sutures. The bulbocavernosus muscles are also united in the midline with interrupted chromic catgut sutures.

Bonney sutures, which may here be called paraurethral fixation sutures, are now placed, one to either side of the urinary meatus. As before, the central portion of these sutures are placed first, to avoid injury to the urethra. The lateral parts of these sutures again transverse the bulbocavernosus muscle. In this manner the terminal portion of the urethra is supported laterally, and the mucosal edges to either side are approximated.

A fourth Bonney suture is placed posteriorly, traversing in similar fashion the mucous membrane of the vagina and that surrounding meatus. This suture is carried deep through the bulbocavernosus and pubococcygeal muscles, lateral to the suburethral reefing sutures previously inserted and tied, emerging on the vaginal mucosa. They are tied in the following order: The two lateral sutures first, then the posterior suture, and finally the anterior suture.

Finally, the remaining gaps in the vaginal mucosa below the meatus are closed with continuous or interrupted sutures of chromicized catgut. The retention catheter is left in place for forty-eight hours.

DISCUSSION

The closing mechanism of the female bladder has been investigated by several methods: dissection, x-ray, and intubation. Deductions for these studies vary as widely as the methods, and none is accepted generally. There is, therefore, no certain physiologic basis upon which the choice of operation in relative incontinence may be urged.

Natvig claims that stress incontinence is due to insufficient support on the part of the muscles and fascia surrounding the urethra. Kennedy believes in the existence of a voluntary sphincter, which may be compromised by direct injury or indirectly through distortion or fixation. Rubin, Newman and Davids state that "incontinence is probably due to incompetence of both the internal or external sphincters." Bonney and Watson assert that laxity of the anterior musculofascial sheath is responsible for stress incontinence, through a loss of the valve-like action at the angle between the urethra and bladder. Thomsen claims to have demonstrated that the closing mechanism is primarily a function of the urethra itself, and only secondarily of its surroundings, the mechanism failing when the angular bend in the urethra (Heiss's loop) is absent. Martius ascribes stress incontinence to defective sphincteric control of the urethra, and describes a lissosphincter and a rhabdosphincter.

It is altogether possible that bladder control may depend upon more than one factor. If this is so, incontinence could result from various types of injury and in some instances, perhaps in many, several factors may be involved at the same time. This would account for the fact that operations based on different conceptions of the mechanism of bladder control have a substantial percentage of both successes and failures. I believe that the most important elements in this operation are the two layers of suburethral sutures and the fact that more of these supporting sutures can be placed when the urethra is lengthened. It

may be argued, however, that Dudley and others have cured relative incontinence by simple elevation of the urethra, without suburethral reinforcement. Moreover, it is well known that cystocele may exist without incontinence and that urinary incontinence may actually occur after a thorough cystocele repair. It would seem, therefore, that suburethral reinforcement is not the only factor in establishing bladder control.

The operation here described has been successful in 17 out of 19 cases which have been followed for sufficient time to be properly evaluated, and appears to be successful in two more recent cases. It is upon this record, rather than on most questions of rationale, that this operation of "paraurethral fixation" for stress incontinence is presented.

I wish to express my appreciation of the fact that I was able to perform this operation upon autopsy material made available by Dr. William C. Wilentz, county physician, and upon five patients from the surgical ward services of Dr. George W. Fithian and Dr. William H. McCormick, Jr.

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THE IMMEDIATE TREATMENT OF OBSTETRIC HEMORRHAGE AND SHOCK*

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PUERPERAL mortality in the City of New York steadily declines, yet puerperal deaths from hemorrhage grow no less. In 1938 there were 357 puerperal deaths, in 97 of which, or 27 per cent, hemorrhage was an important factor. In 1939 there were 320 deaths, and 90 deaths to which hemorrhage contributed, or 35.5 per cent. In the Borough of Brooklyn, if deaths from hemorrhage are combined with those due to accidents of childbirth, as largely due to hemorrhage and shock associated with delivery, we find similar high figures, with but slight improvement in the situation; in 1938 there were 127 puerperal deaths, with 52 deaths, or 41 per cent, due to hemorrhage and shock, and in 1939 a total of 110 puerperal deaths with 42 deaths, or 38 per cent, due to these joint causes.

Our interest in this problem grows with our experience in our Brooklyn obstetric conferences, in which we inquire into the circumstances of puerperal death. Hemorrhage is the outstanding controllable factor in Brooklyn. It is common for patients to receive small amounts of blood or none at all, and in many cases transfusion is performed too late. Frequently no preparations for transfusion have been made, until evidence of shock has appeared. All the details of our 1940 deaths are not yet available for study, yet the bare facts in 6 cases assigned to

*Read at a meeting of the Brooklyn Gynecological Society, February 7, 1941.

hemorrhage, though selected at random, will illustrate the points I wish to make. All these patients were delivered in hospitals.

CASE 1.—In a primipara, aged 25 years, hemorrhage occurred two hours after forceps delivery. Two hours later, a more profuse hemorrhage was followed by shock with blood pressure 64/60. With use of ergotrate, morphine and 1,000 c.c. of dextrose she improved, and blood pressure rose to 122/66. Her condition remained good for three hours, when she died in shock.

CASE 2.—In a para iii, aged 34 years, profuse post-partum hemorrhage was treated by vaginal packing, massage of the fundus, and Trendelenburg position. One-half hour later, the pulse became rapid and thready, and her respirations were shallow, and she was given 2,000 c.c. of 5 per cent dextrose. When systolic pressure fell to 40, she was given caffeine. One hour later, 5 per cent dextrose was repeated, and 200 c.c. of whole blood given. Three cubic centimeters of coramine and 3 c.c. of adrenalin were given before death fifteen minutes later.

CASE 3.—In a para i, aged 29 years, spontaneous delivery was followed by profuse hemorrhage, and 1,000 c.c. of 5 per cent dextrose was given. One hour later another profuse hemorrhage occurred with profound shock. The vagina was packed and 1 c.c. of coramine was administered. An hour later $\frac{1}{4}$ gr. of morphine sulfate was given. Two and one-half hours after delivery, she received 750 c.c. of blood by transfusion. She did not improve, and coramine and adrenalin were given. She died in shock two hours after transfusion.

Three cases of shock following cesarean section follow:

CASE 1.—Primipara, aged 26 years, had a cesarean section after thirty-six hours of labor. Considerable hemorrhage occurred during the operation, and 3 c.c. of pituitrin were given. Shock occurred before closure of the uterine incision. Cardiac stimulants were given, 3 c.c. of adrenalin, 2 c.c. of coramine, 2 c.c. of digifoline, and 500 c.c. of 10 per cent dextrose solution. Transfusion was begun one hour after operation, and 2 c.c. of adrenalin was repeated. She died in shock shortly after transfusion.

CASE 2.—Primipara, aged 24 years, had a cesarean section after a long labor and failed version. Blood loss was estimated at 500 c.c. Shock following operation was managed with 1,000 c.c. of 5 per cent dextrose, coramine, and caffeine. Blood transfusion of 500 c.c. was given, but shock became more profound and death occurred.

CASE 3.—Para i, aged 27 years, shortly after her return to bed following elective cesarean section, suffered a profuse hemorrhage, for which she received 1,000 c.c. of 10 per cent dextrose solution. One-half hour later, bleeding recurred, and the uterus was packed. During the next half hour she bled through the pack and transfusion was attempted. She died in shock.

DISCUSSION

It is not my purpose to examine the conditions and circumstances which give rise to obstetric hemorrhage, or to discuss measures for its actual control. Knowledge of methods of prevention is fundamental, and successful management of serious hemorrhage depends largely upon the skill of the obstetrician and timely replacement of blood loss. We cannot always prevent hemorrhage, or even stop it, yet we can be prepared for it, acutely conscious of its importance as a forerunner of shock.

Every physician has seen shock follow hemorrhage; the cold, clammy skin, ashen cyanotic pallor, shallow respiration, steadily falling blood

pressure, the small rapid pulse which is finally lost, and apathy and unconsciousness just before death. This syndrome is the result of hemorrhage, yet dehydration, long labor, and anesthesia may initiate it or contribute to it, and often precipitate it when blood loss alone would not have done so.

It has been shown that large doses of barbiturates increase anoxia and so contribute to shock. In fact, all analgesics which slow labor and tend to increase the frequency of operative delivery are factors which deserve consideration. Ether particularly increases blood loss by delaying the mechanism of placental separation. The analgesia of nitrous oxide is associated with steadily increasing anoxia, and anesthesia is possible only when all oxygen has been cut out. Spinal anesthesia, if it has not affected the respiratory mechanism, invites disaster by causing vasodilatation no different from that associated with primary or neurogenic shock.

Certainly the best method of treatment of shock is prevention or at least early recognition. Low blood pressure is not an early symptom, but slight decline in the systolic level is of great significance. The pulse rate is soon accelerated, but diminution in the size of the pulse, because of diminished volume flow, is the earliest clinical sign available.

General supportive measures are important. Morphine for restlessness is valuable. Cold blood-soaked linen should be replaced by a warm dry blanket, yet enough heat to induce perspiration will defeat our purpose. Elevation of the foot of the bed at least two feet is valuable for post-partum hemorrhage, and lowering the head of the delivery table will help syncope. Hot enemas are usually not retained. Oxygen is rational for the associated anoxia, while carbon dioxide is not. Adrenalin is useless, perhaps dangerous, since the arteries are already contracted. All cardiac stimulants are contraindicated, since shock is not of cardiac origin.

Saline solution will restore blood volume if plasma loss has not been serious. It is then ineffective. Dextrose likewise passes quickly through normal capillaries. It is clear that large amounts of these fluids may accumulate in the tissues, even though edema may not be evident. These crystalloid solutions are valuable in preventing shock, but useless and perhaps dangerous when it has been established. Hypertonic solutions simply increase dehydration.

The earliest effect of uncomplicated obstetric hemorrhage on the blood is probably dilution, not concentration. Yet that follows soon enough. Whether this is so or not makes very little difference when hemorrhage occurs in the delivery room, for if blood pressure remains depressed, plasma is lost through the capillary walls. Loss of plasma is responsible for the symptoms, whether shock is due to hemorrhage or not. Delay in treatment is serious, for shock may become irreversible and neither blood nor plasma will save the patient. It is of the utmost importance to realize that danger lies less in loss of red blood cells, than loss of blood volume. It is our experience in hemorrhage that response to transfusion is prompt, while in shock it is not.

Restoration of blood volume is logical since in no other way can we maintain circulatory efficiency. Lost blood must be replaced by blood or a satisfactory substitute for blood. Transfusion is clearly indicated, yet it is common for those engaged in obstetric practice to depend upon everything else, and transfusion is not widely used. There are good reasons for this. Blood is hard to get. Professional donors for the large amounts needed are expensive, and relatives and friends have to be found before they are typed and crossmatched. Disappointments are common. We have found that preparations for transfusion take almost two hours, unless the donor is already in the hospital. Since citrated blood, because of its readiness and ease of administration, meets all the requirements of the obstetrician, blood banks are ideal, yet even they are not certain sources of supply even in large hospitals.

The result of dehydration and serious hemorrhage is loss of circulating blood volume. Unless plasma colloids are sufficient to maintain volume, aqueous solutions will not be retained in the blood stream, and their continued administration will further reduce blood volume. With reduction of blood pressure to critical levels, stasis and blood concentration occur. Then use of plasma, not cells, is indicated. Acacia, because of its colloidal properties, is far superior to crystalloids, yet it cannot be recommended unreservedly at present. In 500 c.c. of plasma, there is twice as much plasma protein as in an equal amount of blood. Red cells may be replaced later when blood is available.

Plasma or serum are ideal substitutes for blood. Simple and easy to prepare, no typing or crossmatching is necessary, and either may be given repeatedly in large amounts without fear of untoward reaction. Plasma is prepared by centrifuging citrated blood at high speed, or simply by sedimentation in a refrigerator for at least five days. Blood that is in process of settling may be shaken up and administered as blood, if of the proper type. The source is voluntary donors, and the average yield of 500 c.c. of blood to which 70 c.c. of 2.5 per cent sodium citrate has been added is well over 250 c.c. It is used with an equal amount of saline, though this is not necessary. Serum may be secured by suction by simply allowing withdrawn blood to clot; the yield is less, and it may cause an urticarial rash if it has not been pooled. Serum is clear. Plasma may be cloudy due to lipoids, fibrin veils, or precipitates which must be filtered out.

A plasma bank is practical for even the smallest hospital, while a blood bank is not. It is a convenient, quickly available fund for modern shock therapy, for plasma may be stored for a long time and be safe for use. Vacuum collection and administration is best. If tube and needle sets are properly cleansed, no reactions will be reported from its use, and autotransfusion will finally disappear from obstetric practice. Plasma cost is negligible. Those lying-in institutions without facilities for transfusion, no microscope, stale typing sera or none at all, no one in attendance able to type or crossmatch blood will soon have no excuse, for blood serum for emergencies is already commercially available.

Obstetric hemorrhage is so dangerous, so deadly, that its immediate treatment is of the utmost importance. The patient may die. Or loss

of blood, not sufficient to cause death, may predispose her to subsequent infection, from which she may die or suffer prolonged morbidity.

The role of hemorrhage in death from sepsis is an important one. We should be prepared for hemorrhage and shock before, during, and after every labor we conduct.

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256 JEFFERSON AVENUE

SUPRAVESICAL EXTRAPERITONEAL CESAREAN SECTION (WATERS' OPERATION)*

THE RESULTS IN 17 CASES

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SINCE 1824, when Physick¹ first described an extraperitoneal approach to the lower uterine segment, there have been various techniques set forth by many operators, in attempts to reduce tissue trauma and to avoid opening the peritoneum by simplifying the technique. It has been proved that peritonitis complicating this type of section, of which the Latzko was the most popular, is extremely rare. In 1940 Waters² described an extraperitoneal operation whereby he was able to reach the lower uterine segment by dissecting the peritoneum from the bladder fundus. His approach seemed logical, not too complicated, and he gave an excellent description of his procedure.

Recognizing the advantage of this procedure in potentially and actually infected cases where abdominal delivery was desirable, and having been disappointed by the maternal injury and frequent fetal sacrifice so commonly found in difficult forceps and hazardous version delivery of such cases, a study of this new technique was undertaken. Two years prior to this, the Latzko operation had been done in frankly infected cases, but, because of the limited exposure and the proximity of the ureter and uterine artery, difficulty was constantly encountered.

Quoting Waters "The indication for a true extraperitoneal operation is the probable or actual existence of intrauterine infection. If properly done, it should largely remove peritonitis as a cause of postoperative mortality, and at the same time it conserves the uterus." He refers, of course, to patients whose delivery by section is imperative. With this as a background 17 patients were operated upon by the supravescicular approach.

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INDICATIONS	NO. CASES
Cephalopelvic disproportion	12
Dystrophy dystocia syndrome	3
Premature rupture of membranes (18 hours' duration) and fetal distress in a diabetic with 2 previous stillborn infants	1
Pre-eclamptic toxemia with placental separation (labor 6 hours)	1

Thirteen of the 17 patients were primiparas and 4 multiparas. Three had previous laparotomies. Seven patients had ruptured membranes. Three had severe nonspecific vaginitis, one showing a luxuriant growth of condylomata acuminata around the vulva. One had a fever of 102.4° F. on admission. The average length of labor prior to delivery was seventeen hours with a range of from three to forty-three hours.

Extraperitoneal section was indicated in all but 3 cases. These 3 patients needed section because of platypelloid pelvis in 2 instances and android pelvis in 1. They were not infected, were not in labor and the membranes were intact, but it was felt that to develop our technique, the performance of extraperitoneal section was justified. Their post-partum courses were uneventful except for a slight wound infection at the drainage site. They were discharged from the hospital on the twelfth, thirteenth, and thirteenth day, respectively.

OPERATIVE DIFFICULTIES

Three significant maternal operative difficulties were encountered: The first and most frequent was puncture of the peritoneum prior to extraction of the infant. This occurred in all 3 patients having low abdominal scars, and in 6 of the remaining cases. In most instances, it was possible to purse-string the peritoneal opening and prevent contamination at the time of fetal extraction, or, as in the cases previously operated upon, to do a laparotrachelotomy. As we became familiar with the technique, however, this complication was avoided.

The second was hemorrhage due to varicosities of the lower uterine segment.

The third was laceration of the bladder. This occurred in a patient who had been previously operated upon because of ectopic pregnancy and who had developed a thick keloid scar. With constant bladder drainage for eight days, the wound healed and the patient was discharged on her fourteenth post-partum day.

Four patients were delivered by low cervical section after attempting the extraperitoneal technique. Two of these 4 cases were our first attempts and the other 2 had low midline scars which made anatomic dissection impossible. Their post-partum courses were not unusual in any respect.

Because of the difficulty encountered in operating upon the 3 patients who had had previous lower abdominal operations, such scars are listed as possible contraindications to this type of operation.

POSTOPERATIVE CARE

Generally speaking, this was the same as is usually found after cesarean section. However, as most patients were hungry and peristalsis was present within twenty-four hours after operation, a full

liquid diet was given on the first day, soft on the second, and a regular diet on the third day. Neoprontosil was given intramuscularly in frankly infected cases. Blood transfusion was resorted to as needed. Most of the patients voided around the catheter on the second day and after that voluntarily. A two-day check for residual urine was routine. A gutta percha drain was placed in all wounds except 2. This was removed between the second and fourth days, depending on the amount of oozing at the time of operation and infectivity of the case.

POSTOPERATIVE COMPLICATIONS

Six patients showed no morbidity. Post-partum days averaged 16.8, with a range of from twelve to thirty-four days. The latter patient had a small gynecoid pelvis, a temperature of 102.4° F., a pulse of 140, and had been in labor twenty-one hours at the time of admission. Her convalescence was complicated by wound infection and bilateral thrombophlebitis. In 6 instances the urinary tract was infected. The substitution of a No. 16 plain catheter for a mushroom catheter and the removal of it forty-eight hours postoperatively reduced the frequency of this complication. One patient, with varicosities of the lower uterine segment, had a severe wound infection resulting in uteroabdominal fistula which closed spontaneously before discharge from the hospital. One patient, with bronchitis on admission, developed postoperative pneumonia but was discharged on the fifteenth day. Considering the type of cases operated upon, the absence of peritoneal irritation or infection is worth comment. In fact, postoperative distention was noted only once, and peristalsis was invariably present within twenty-four hours after operation.

MORTALITY

There was no maternal mortality, and no neonatal deaths. The infants ranged from 2,535 to 4,120 Gm. in weight; the former was delivered from a diabetic mother when signs of fetal distress developed eighteen hours after premature rupture of the membranes.

FINAL EXAMINATION

The results of the six weeks' follow-up were most gratifying. Of the 10 patients returning for examination only one complained of tenderness on palpation in the vesicouterine area. The parametrium was normal in 8 cases and slightly thickened in 2. The uterus was freely movable in all cases; 2 were in second-degree retroversion and one was subinvolved. The absence of pelvic peritoneal adhesions was general.

One patient is now seven one-half months pregnant, and we plan on delivering her by low cervical section.

SUMMARY

1. In this small series of 17 cases, there was no maternal or infant mortality. Peritoneal irritation and peritonitis were absent.
2. Laceration of the peritoneum and bladder must be guarded against.
3. Follow-up examination showed only occasional thickening in the left parametrium, with the uterus always movable, usually small and forward in good position.

4. Notably lacking were the effects of trauma and infection that invariably follow difficult forceps and difficult version delivery of such cases.

5. A pre-existing lower midline scar may be a contraindication to extraperitoneal section; in which case an exclusion type of operation or laparotrachelotomy can be substituted.

6. The number and severity of post-partum complications was in direct proportion to the degree of genital infection and in indirect ratio to the operator's skill in performing this procedure.

CONCLUSIONS

The supravescical cesarean section as described by Waters offers a safe means of delivery in neglected and questionably or frankly infected cases in which a section is imperative.

We wish to express our appreciation and thanks to Dr. Charles E. Ziegler for his constant help and guidance in the selection and care of these cases.

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TWO UNUSUAL CASES OF CHORIOEPITHELIOMA*

1. A VERY YOUNG MYOMETRIAL CHORIOEPITHELIOMA FOUR MONTHS AFTER A HYDATID MOLE IN A PRIMIGRAVIDA OF TWENTY-THREE YEARS
2. AN ADVANCED CHORIOEPITHELIOMA LOCALIZED IN THE CERVIX IN A GRAVIDA XVII OF FORTY-FOUR YEARS WITH NO ANTECEDENT HYDATID MOLE

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THE diagnosis of chorioepithelioma has been much facilitated since we have learned to utilize the Aschheim-Zondek test and the Friedman modification. The quantitative test has, moreover, proved particularly valuable in detecting the presence of malignant chorion at an early stage. The persistence of positive Friedman tests in instances where the uterus has been emptied of its contents whether gestational or hydatid mole suggests the presence of chorionic invasion either of the genital area or in remote places of the body. This is well demonstrated by the following case which, on account of the youth of the patient, also presented a surgical problem of unusual interest.

CASE 1.—D. P. (Admission No. 397746), a 23-year-old, unmarried nullipara, was admitted to the Gynecological Service of Mt. Sinai Hospital Aug. 29, 1936, with the following history: Her menses began at 14 years of age, recurring regularly every twenty-eight days and of six days' duration, with the exception of one year (1933) when they were delayed for two to three months, accompanied by dysmenorrhea. An appendectomy in 1933 was the only operation she had undergone, following which the menses again became regular. Her last normal period occurred on March 1, 1936. She missed her regular period in April and on April 18, after a menstrual delay of two and one-half weeks, she visited her private physician who informed her that she had a retroverted uterus, which he tried to correct by passing a sound. The patient considered herself pregnant. After the instrumentation there followed

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profuse vaginal bleeding which continued until her admission May 8 to the New York Hospital. By curettage a hydatid mole was removed from the uterus. The Aschheim-Zondek test at this time was said to be negative.

Following her discharge from the hospital the vaginal bleeding continued and on June 26 she was again curetted. The Aschheim-Zondek test was positive in a dilution of 1:10. The pathologic report of the curettings was syncytioma.

Despite the last curettage, the bleeding continued. On August 10 a third curettage was performed. The Aschheim-Zondek test was positive in a dilution of 1:50. The pathologic report was chronic endometritis. Bleeding continued for a week longer, finally stopping August 19.

At the time of her admission to Mt. Sinai Hospital ten days later, the patient was entirely symptom free. Because her urine still showed a positive pregnancy test in a dilution of 1 in 20, Dr. Phineas Bernstein referred her to the hospital for further study.

The patient was well developed and well nourished. Her blood pressure was 120/80. The general physical examination was negative. The external genitalia were normal. The cervix was of normal size and consistency. The uterus was not appreciably enlarged; it was soft, retroverted, and retroflexed. The adnexa were not palpable. The parametria were negative.

The hemoglobin was 80 per cent; the sedimentation time two hours, ten minutes. The Friedman test on September 2 was positive with 1 c.c. of urine (1 in 20); 0.1 c.c. of urine was negative. This was approximately six months following her last normal menstrual period. X-ray film of the chest was negative.

Although the uterine bleeding had subsided for the past twelve days and the patient had no complaints during her observation at Mt. Sinai Hospital, the gonadotropic principle of the urine of pregnancy was present in a concentration which indicated the presence of active chorion epithelium in the genitals or in some remote place. The most common metastatic depot, the lungs, did not as yet show any lesion on the x-ray film.

The question resolved itself into two procedures: One to continue the policy of watchful waiting, and the other, surgical exploration.

As a fourth exploratory curettage in my experience would most probably again fail to disclose a small lesion which could readily escape the curette I decided to do a laparotomy and to inspect the uterus, adnexa, and adjacent viscera and, in case of doubt, to incise the uterus.

Accordingly, a laparotomy was done September 10. The findings were: an extremely soft, mottled grayish, vascular uterus which was slightly enlarged to about the size of a six weeks' gravidity. The right ovary contained a large corpus luteum cyst the size of a peach. The cyst broke in the attempt to deliver it. The left ovary was only slightly larger than normal and contained several small lutein cysts. It was adherent to the tube and the broad ligament.

Procedure.—As a preliminary step, the broad ligaments were securely clamped to minimize uterine bleeding and to prevent extension of the lesion via the lymphatics and blood stream. The fundus of the uterus and anterior uterine wall were then incised and the endometrial cavity and tubal angles examined. A positive diagnosis of chorioepithelioma could not be made on gross examination. However, the uterus was definitely abnormal. The endometrium was exceedingly friable and one small area looked suspicious. The myometrium was edematous, flabby and contracted under the examining finger. There were several small ecchymotic and hemorrhagic spots on the peritoneum, suggesting endometriosis. The uterine muscle also suggested the same abnormality. For these reasons and because of the positive pregnancy test, a supravaginal hysterectomy including bilateral salpingo-oophorectomy was performed.

Pathologic Report.—The specimen consisted of a supravaginally amputated uterus and both adnexa. Only a portion of the right ovary was attached to the specimen. The rest was received separately in fixative. Uterus appeared normal in size; measured 7.5 by 6.5 by 3.25 cm. Serosal surface was smooth. On the posterior surface near the lateral border and on the anterior surface near the lateral border, there were small superficial adhesions which had a brownish hue and resembled the tobacco-stained appearance of endometriosis. Uterus felt somewhat soft. On section the myometrium was 2 cm. in thickness, pink gray in color, rather homo-

Of the positive cultures, only 27.7 per cent had corresponding positive slides; 19.8 per cent had clumps of typical extracellular diplococci; 8.0 per cent had scattered typical extracellular diplococci; and 44.5 per cent had completely negative smears. Only four smears with intracellular organisms and nine smears with typical extracellular organisms had corresponding negative cultures (0.56 per cent), in spite of the fact that there was frequently a delay of two or three hours in the inoculation of plates and an interval of four to five hours before incubation.

When cervical and urethral smears and cultures are compared separately, the results are even more striking (Table VII). Urethral smears are considerably less reliable than cervical smears as an indication of

TABLE IV

DATE	CHICAGO MUNICIPAL SOCIAL HYGIENE CLINIC		CHICAGO LYING-IN HOSPITAL							TREATMENT AND PROGRESS NOTES
	SMEAR	CULTURE	Hb	BL. LEVEL	SMEAR		CULTURE		DRUG AND DOSAGE SULFANILAMIDE	
					CERVIX	URETHRA	CERVIX	URETHRA		
1/30/40	+		70%		E Few	- Shreds	3+	3+	4 Gm. p. 4	Vaginal discharge, endocervicitis
2/ 2/40					- Few	- Epith.	2+	2+		
2/ 6/40	-		75%	4.6 mg.	- Few	- Epith.	+	-	3 Gm. q. 4	Moderate cervical discharge
Post-menstr.										
2/13/40	-				- Occ.	- Few	+	+		Missed drug one day. Urethra clean. Cervix inflamed
2/16/40					- Mod.	- Few	og.*	og.*	Dis-cont.	Slight discharge
2/23/40					- Epith.	- Epith.	-	-		Slight discharge

*Og. = overgrown.

TABLE V. POSITIVE CULTURES AFTER SMEARS HAD BECOME NEGATIVE

PATIENT'S NUMBER	NO. OF DAYS	SITE
311	126	Urethra and cervix → Cervix
314	50	Cervix
316	23	Urethra and cervix
320	19	Urethra and cervix → Cervix
321	25	Cervix
328	86	Urethra and cervix
359	49	Urethra and cervix
375	36	Urethra and cervix
396	33	Urethra and cervix
423	51	Urethra and cervix
426	33	Urethra and cervix
452	30	Urethra and cervix

It occupied the entire inner circumference of the cervix, the lips of which were thinned out and at the left side presented a grayish yellow membrane about 3×4 mm. in thickness which covered part of the protruding mass and was intimately adherent to the cervical mucosa (Fig. 4). Part of the tumor was removed by ovum forceps; the rest of it was curetted and the membrane was excised. There was considerable bleeding during this procedure. The uterine cavity appeared to be empty except for a few small fragments which may have had some of the characteristics of the tumor lying within the cervical canal. It was my impression that these fragments were removed from near the internal os. The latter was about the width of a lead pencil. It was dilated to permit curettement. There was a sharp line of demarcation between the internal os and the tumor-bearing portion of the cervical canal.

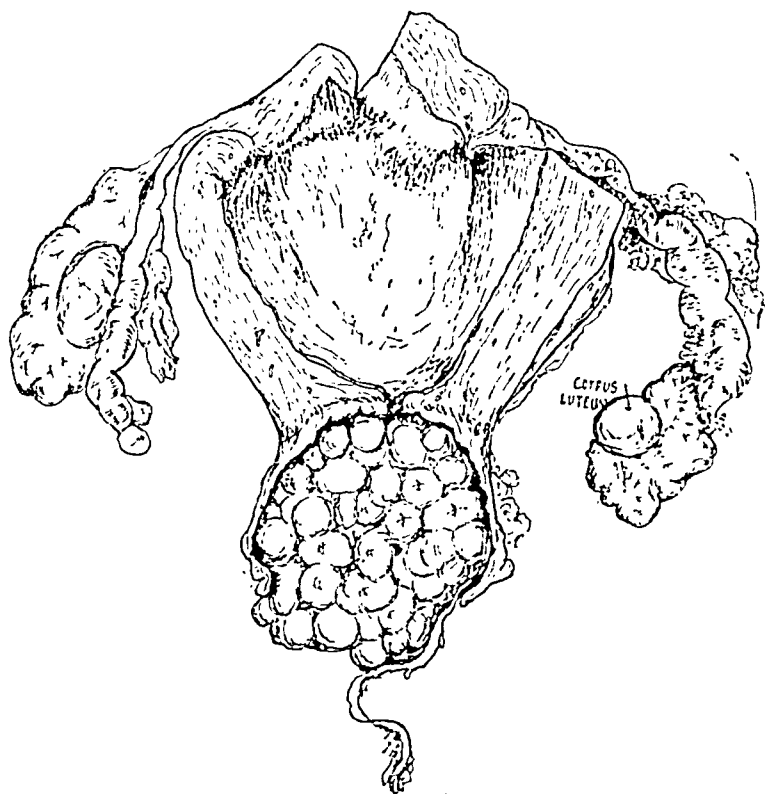


Fig. 2.—Diagrammatic sketch of uterus, showing the chorioepithelioma limited to the cervical area.

The nature of the lesion was not clear even at this stage. Its localization and its apparent origin from the cervix threw doubt upon the diagnosis of a placental polyp or of an aborting mole. Yet it resembled either of these closely. On the other hand, it was too easily removed for it to be a cervical carcinoma. There was no antecedent history of hydatid mole. Her last miscarriage at six months took place July, 1939, followed by curettage. Her periods had apparently been normal until three months preceding her present attack. After two months amenorrhea, irregular bleeding began and continued for a month. Although chorioepithelioma was considered, there were no other corroborative signs or symptoms to support this diagnosis. Only the laboratory examination of the fragments from the cervical tumor revealed the presence of chorioepithelioma. Decidua was found but no villi. An excised portion of cervix showed no significant changes.

Before the hysterectomy was carried out, a catheterized specimen of urine was sent to the laboratory for a Friedman test. Although obtained five days following the first operation, the urine did not contain the gonadotropic hormone in strengths of 5 c.c., 0.1 c.c., 0.075 c.c. and 0.005 c.c.

At the laparotomy, the uterus was found to be about the size of a five or six weeks' gravidity, purplish in color and soft. The adnexa appeared normal. There

geneous. From gross inspection at this time, there is no evidence of abnormal myometrial infiltrations. Endometrial cavity measured 5.5 by 3 cm. It had a slightly shaggy appearance, but the endometrium did not appear thickened grossly in any particular area, except in each cornu where it appeared slightly thickened. In the cervical canal about 0.5 cm. beyond the distal cut margin, a small pin point bluish area could be seen beneath the mucosa.

The left tube was normal in size, length, and configuration. Its patency could be demonstrated. Left ovary appeared slightly enlarged and measured 4.25 by 3 by 1.75 cm. A few fine adhesions were present in its inferior border. On section through the ovary, there were present small cystic follicles and one follicle cyst which measured 2.5 cm. in diameter. The wall of this cyst was somewhat hemorrhagic. At the outer pole, there was a corpus luteum which measured 1.5 cm. in all directions.

Immediately following the operation, the Friedman test was positive with 1 c.c. of urine. Six days following operation 20 c.c. of urine gave a negative Friedman test, and the same result was obtained by repeated tests throughout her stay at the hospital fifteen days after operation. The postoperative course was uneventful.

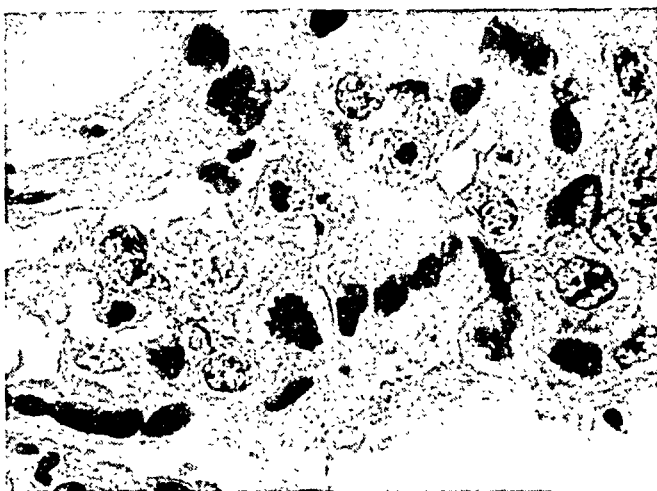


Fig. 1.—High power showing three mitoses in the center. (Case 1.)

The first pathologic report was: Chronic endometritis with hyperplasia and adenomyosis; corpus luteum cysts of the ovaries; old hemorrhage on the pelvic peritoneum. Inasmuch as the Friedman test became negative after the operation, Dr. Otani also felt that the lesion must reside in the uterus, hence he continued to make serial sections (over 200 sections) which revealed the small chorioepithelioma as shown in Fig. 1.

This patient was observed until Feb. 11, 1938, during which time the pregnancy test on urine was negative. She had had a radical mastectomy of the left breast February 1 for a carcinoma simplex which had no relationship to the original tumor.

CASE 2.—This is in marked contrast to the first. It concerns a 44-year-old woman who had 17 pregnancies, 13 of which were full-term children and 4 resulted in miscarriage. The oldest child is 25 years old, the youngest 8 years. She was brought into my office by automobile, requiring eight hours' ride from Hampton Beach, N. H., where she had had a hemorrhage five days before. She was bleeding profusely; the blood had soaked through the pads and leaked down to the floor.

A quick examination revealed the vagina filled with large blood clots and fluid blood which when cleared away exposed a dark purplish-red polypoid tumor projecting from the cervix. The vagina was tightly packed and the patient was sent to the hospital. Her hemoglobin was 68 per cent. The lesion looked like a placental polyp or possibly an extruding molar pregnancy. Under anesthesia it was possible to examine the lesion more closely. It was found to be somewhat friable and intimately adherent to the thinned-out dilated cervix which admitted the finger readily.

which were very superficial. There was a bridgelike area of tissue which measured 1 cm. in width and covered over a tunnel of cervical mucosa. This area was 2 cm. from the external os. There was a cuff of the portio of the cervix included with the specimen which showed no gross changes. The right ovary was normal in size. The outer surface was slightly corrugated but smooth. On section, the ovary showed a normal pinkish yellow appearance with evidence of an old corpus luteum near the outer pole. The Fallopian tube on the right side measured 10 cm. in length; fimbriated extremity was open and the lumen of the tube was patent throughout its length. The tube showed no gross abnormalities. On the left side, the ovary was approximately the same size. The outer surface likewise showed no gross abnormalities and on section the ovary had a typical yellowish pink appearance with few tiny thin-walled cysts and 2 yellowish plaquelike areas, one about the size of a pinhead and the other the size of a split pea. Received separately in fixative were 3 masses of tissue which were removed from the parametria.

The pathologic report was as follows: A small remnant of chorioepithelioma was found in the endometrium near the cervical canal (Fig. 4). The uterus otherwise showed no evidence of tumor, despite numerous sections which were made from various portions of the uterus. One ovary showed a corpus luteum. Adenomyosis of the uterus was present.

Two subsequent Friedman tests, September 19 and December 12, proved negative. The patient was seen Jan. 14, 1941, and appears well.

SUMMARY

In the first case, the chorioepithelioma was very small and was localized in the myometrium. It occurred after a hydatid mole which resulted from the first pregnancy in an unmarried woman of 23 who two years later had her left breast removed for a carcinoma simplex. The Aschheim-Zondek test was positive in this case in a dilution of 1:50, which is not abnormally high as the gonadotropic hormone has been found in Dr. Frank's laboratory in concentrations of 0.075 and 0.05 in normal pregnancy. The Friedman test was negative five days after the removal of the uterus. This fact was significant enough to stimulate the pathologist to attempt to find the lesion which he actually discovered by making some 200 sections from the uterine wall, after the ordinary routine laboratory study had failed to reveal the lesion.

The second case was that of a woman of 44 years of age who had had 17 pregnancies (13 children and 4 miscarriages), the last pregnancy a year ago which terminated in a miscarriage. The chorioepithelioma was not preceded by a hydatid mole. It was localized to the cervix. Its origin was in all probability from the isthmus of the uterus or from the cervix at the internal os and resembled a placental mole in the process of extrusion, as both from the observation at the time of the curettage and the study of the uterus itself, no remnants were found in the uterine cavity where it is most commonly located.

I have seen several cases where the first evidence of chorioepithelioma was in the lungs and no lesion in the uterus discoverable, while in others the metastatic chorioepithelioma was located in the perineal area and vagina without any evidence in the uterus. One such case which I saw several years ago had a metastasis in the jejunum which was discovered some months later at autopsy.

As to the Aschheim-Zondek and Friedman tests, when either of these is positive, it indicates the presence in the body of active chorionic tissue. The concentration in the urine of the gonadotropic principle does not appear to depend upon the size of the tumor although an excessive amount may be assumed for highly malignant activity. In the first case, the concentration at its highest point was 1 in 50. The test appears to become negative very soon after the lesion in the genitals has been removed, indicating at the same time that no metastasis is present. A careful follow-up for an indefinite period is advisable. The diagnosis and treatment of chorioepithelioma require not only the test for the hormone of chorionic derivation but also well-established x-ray, surgical, and other laboratory technical procedures.

was some induration at the parametrial bases. A typical complete hysterectomy was done with iodoform gauze drainage of the subperitoneal space. Several nodules the size of a pea to a cherry, hanging from the wall of the sigmoid, were removed. They proved to be lymph cysts.

The specimen consisted of a totally resected uterus and both adnexa received in open state. The uterus was enlarged to the size of a six weeks' gravidity and measured 12.5 by 5.5 by 4 cm. Serosal surface of the uterus was smooth and glistening. The uterus had been opened along the anterior wall. The myometrium averaged 2.5 cm. in thickness. It was generally yellowish pink and uniform in

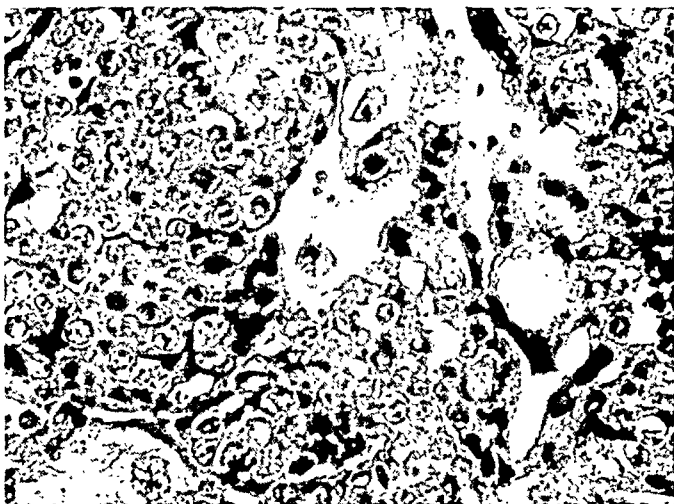


Fig. 3.—High power view of the excochleated tumor. (Case 2.)

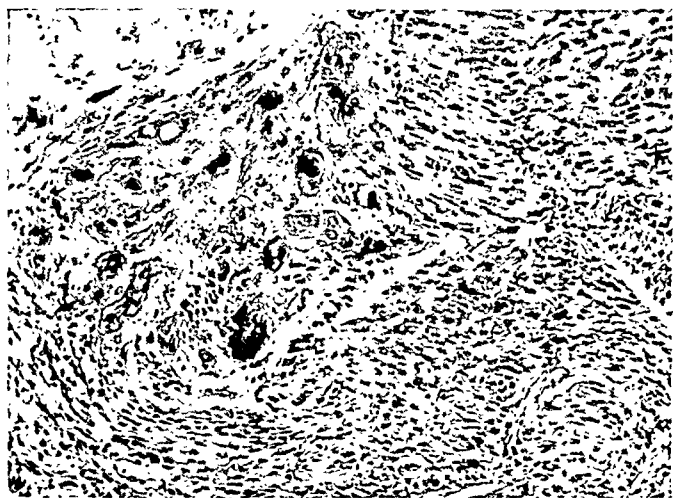


Fig. 4.—Shows syncytial giant cells from the small area near the internal os shown in Fig. 2.

appearance. There were no palpable tumors in the myometrium. The endometrial cavity measured 6 cm. from fundus to internal os and the endometrium had been largely denuded by a previous curettage. The endometrial surface was generally yellowish pink with irregular scattered superficial hemorrhagic areas. The endometrial surface was slightly roughened but no friable or necrotic masses were adherent to it. The cervical canal measured 4 cm. in length and showed a moderate distortion of the normal pattern of the arbor vitae. On the anterior wall, there was a small collection of mucus just beneath the cervical mucosa. The superficial aspect of the endocervical canal showed multiple, irregular, hemorrhagic areas

duration, and considered the test to be more accurate with longer periods of abstinence. It is difficult to follow this in a hospital routine, so the maximum period of concentration in this series was fourteen hours.

Fairly strict precautions were observed to forestall any break in the routine as described above. All specimens were catheterized samples to prevent any error from incompletely dried receptacles. We used a hydrometer certified by the manufacturers for urinary examinations, and checked against water on each occasion it was used. The presence of albumin was determined by Robert's reagent, but no

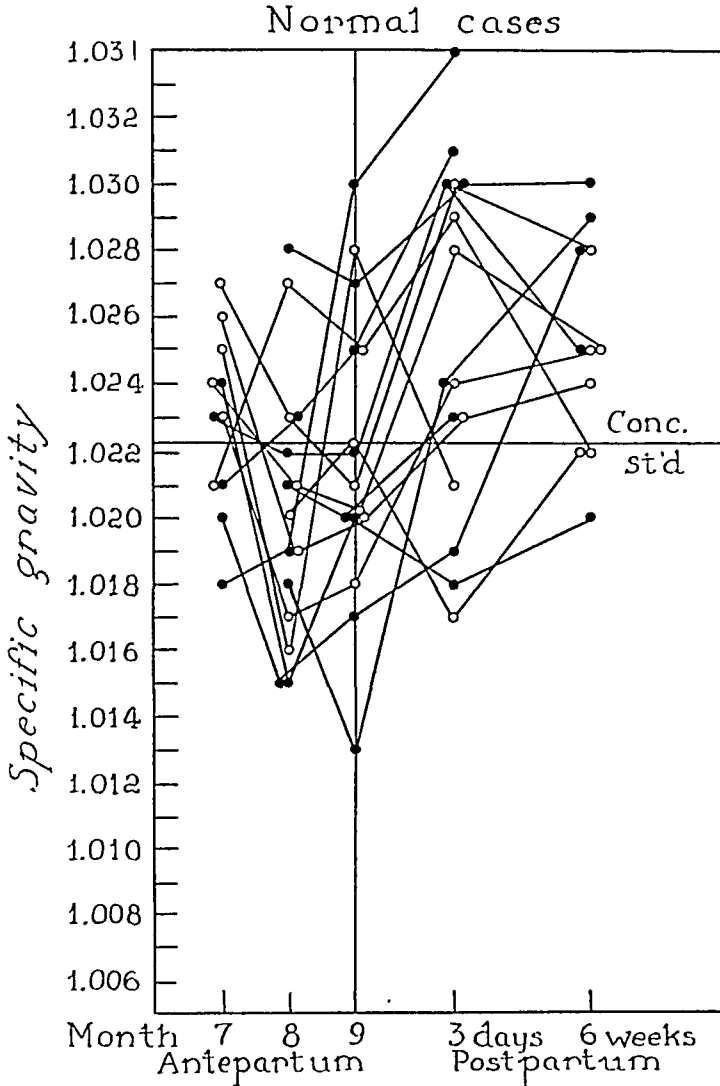


Fig. 1.

quantitative determinations were made. All tests were made on specimens which were at room temperature. The total quantity of urine was not recorded.

The heart and lungs were examined only on the first visit. A blood pressure determination and ophthalmoscopic examination were made at each ante-partum visit.

An effort was made to have the first visit coincide with the seventh month of pregnancy, the second falling in the eighth, and the third in the last month. Two post-partum examinations were made, the first three days and the second six weeks to several months post partum.

Twenty-one patients in all were studied, 14 being multiparas and the remainder primiparas. In the seventh month 15 were examined. The entire group was in-

RELIABILITY OF THE FISHBERG CONCENTRATION TEST IN NORMAL PREGNANCY AND THE PUERPERIUM

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THE Fishberg concentration test of kidney function is rather generally used because of its simplicity and accuracy. It has been employed for many years in this clinic in the study of the pathologic conditions of pregnancy where there is a question of lowered renal performance. It was decided to apply this test to a small group of normal women in the last trimester of pregnancy and the puerperium, in an effort to determine its dependability.

In reviewing the literature it was found that several investigators were skeptical as to the value of the concentration test of renal function in pregnancy.

Dieckmann¹ stated, "The normal pregnant woman is able to excrete urine with an average specific gravity of only 1.022 after a fifteen-hour fast." He believed this to be due to an excess amount of water in the tissues or physiologic edema. In his opinion, the low specific gravity in pregnancy is due to a decreased amount of solids, especially urea and chlorides. Stander² concluded that in normal pregnancy the average variation in the Mosenthal concentration test agreed fairly well with the normal nonpregnant woman, but that there were marked individual variations. In his opinion, the test was not particularly reliable. Hurwitz³ found that several normal pregnant patients failed to concentrate urine to 1.025, although none of these individuals showed any abnormalities in the urea clearance test. Other authors, namely, Janney and Walker,⁴ and Crabtree,⁵ believed that water excretion in the normal pregnant woman is impaired rather markedly. On the other hand, Fishberg⁶ was of the opinion that "the renal function was rarely if ever seriously impaired by the true kidney of pregnancy." He also stated that "the concentrating ability of the kidney was good."

The patients chosen for the investigation were drawn from the Obstetrical Clinic of the Henry W. Grady Memorial Hospital, White Unit, Atlanta, Georgia. This clinic is affiliated with the Emory University School of Medicine. There were 21 patients in all, and of these, all were considered to have a normal pregnancy and puerperium, with the exception of 6. The abnormal patients were included, because it is not always possible to foretell in advance whether a patient is to have a normal pregnancy or not. The Fishberg concentration test was done in accordance with accepted instructions as outlined in his textbook, *Hypertension and Nephritis*. The following is a brief description:

The patients were admitted to the hospital overnight, and their evening meal was eaten at 5 P.M. on the day before the test. This consisted of the regular hospital diet and only one glass of water or milk. No additional food or water was ingested until after the completion of the test. All specimens voided until midnight were discarded. The first specimen to be examined was obtained at 5 A.M., the second and third at 6 and 7 A.M., respectively. The patients were in bed throughout the period of examination. Fishberg⁶ advised a fasting period of sixteen hours'

hypertensive disease and the other had mild pre-eclampsia. Figs. 1 and 2 are used to show the results in both the normal and the abnormal groups.

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THE VALUE OF CONTRACEPTION IN THE CLINIC PATIENT

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IN ANY attempt to evaluate the efficacy of contraception in a group of patients, it is necessary to consider the type of patient as well as the type of contraception. In this study, all of the patients were of the low income group, most of them negroes, and some of them well below the general intellectual level of the community.

Three groups of patients were considered. The first, a group of 24 patients, were suffering with severe hypertensive cardiovascular disease, with or without renal involvement, or had been followed through repeated toxemic or eclamptic pregnancies. Further pregnancies in this group, it was felt, would be extremely hazardous to the health and life of the mother, even with the most meticulous prenatal care.

The second group of 24 control patients were followed by the Charlotte Maternity Clinic for periods averaging eighteen months. The patients received no contraceptive advice, material, or even suggestions. These patients were, or had been, equally ill, and clinically comparable to the first group. Their failure to return to the clinic following delivery accounted for the fact that no contraceptive advice was given.

The third group was comprised of 56 patients, for whom contraception was felt advisable, either for "spacing," chronic disease, or deficiency states. All of the patients, with the exception of the control group, were referred from the Charlotte Maternity Clinic to the Birth Clinic of the North Carolina State Board of Health, operated in connection with the Charlotte, N. C., Health Department. The Charlotte Maternity Clinic, operated in connection with the Duke University School of Medicine, follows approximately 800 to 900 pregnancies per year without cost to the patient. Information and material at the Birth Control Clinic is dispensed by a public health nurse, who works under the direct supervision of a group of physicians of the Health Department and the Maternity Clinic; this group decides after appropriate examination the type of and necessity for contraceptive advice. The method used by the patients in this survey is the so-called "sponge-

vestigated in the eighth and the ninth months and third day post partum. Sixteen patients returned for a final examination, during a period varying from six weeks to several months post partum. All the patients were delivered of full-term infants. Of the entire group, all had a normal pregnancy and puerperium with the exception of 6 cases. These included 4 cases of mild pre-eclampsia and two cases of hypertensive disease. The classification of toxemias used is that suggested by the American Committee on Maternal Health.

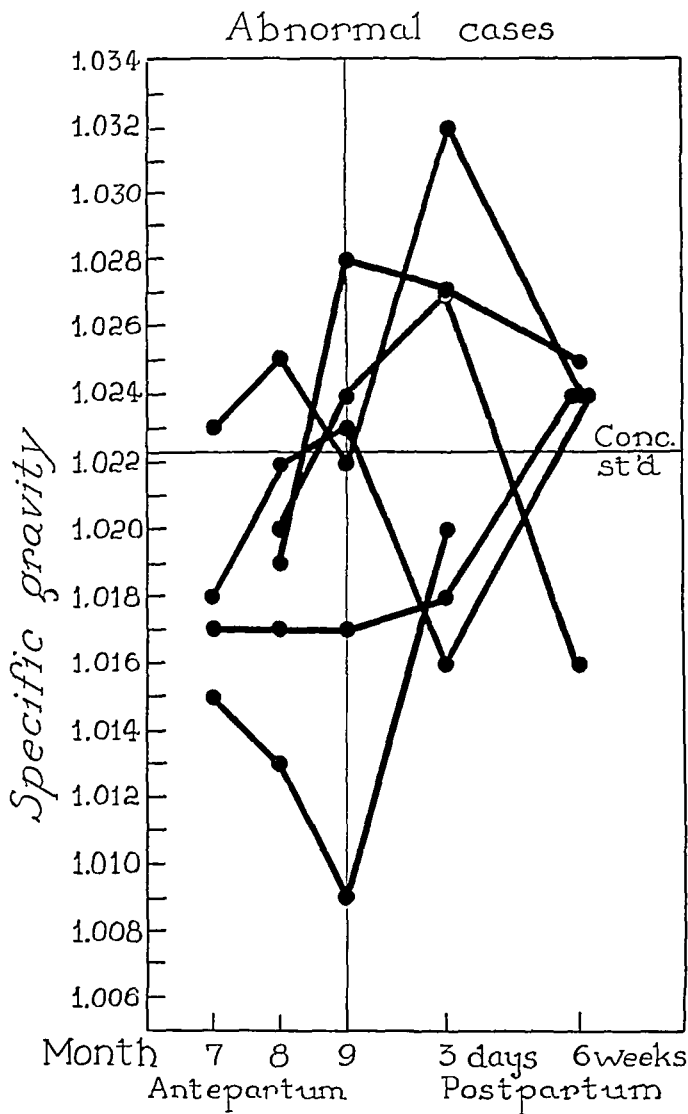


Fig. 2.

Fishberg⁶ gave his standard of concentration as being normal where at least one specimen of the three had a specific gravity exceeding 1.022. It was found that in the seventh month of the 15 patients studied, 7 concentrated to this figure. In the eighth month 5, and in the ninth month 9 of the 21 patients reached this concentration level.

Three days post partum, 14 patients of the entire group concentrated as required. Six weeks to several months post partum, 12 of a total of 16 patients who returned reached the stipulated figure.

Nineteen patients of the entire 21 demonstrated a post-partum increase in their concentrating ability. Of the 2 who did not, one was a patient classified as having

This group of patients had undergone from one to ten previous pregnancies, with an average of four. Their ages were from seventeen to thirty-seven, with an average of twenty-six. The group of 56 patients referred for chronic disease, "spacing," etc., had experienced from 1 to 15 pregnancies prior to their referral, with an average of 5. They ranged in age from seventeen to forty-one, with an average of twenty-eight.

The technique advised and demonstrated is perhaps the most simple, economical, and suitable for this type of patient of any known at present. In no case was there any difficulty in comprehending the technique or procuring the material. None of the patients desired further pregnancies. The various reasons for discontinuing or not employing the contraceptive methods were "too much trouble," "husband dislikes the idea," or no reason at all. It was apparent, however, that the individuals were not sufficiently interested to carry out any contraception for any length of time.

The hypertensive group represents definite potential mortality or morbidity for subsequent pregnancies, and the burden is on the clinic to prevent these pregnancies from occurring. A return of almost one-half of these patients in a pregnant state, usually in the late middle or last trimester, is a definite factor in the continued high mortality in the hypertensive individual.

Corbet, R. M.: *A Visit to Certain North American Clinics*, Irish J. M. Sc., p. 59, February, 1940.

A tour was organized by the Gynaecological Club of Great Britain and Eire at the invitation of the Gynaecological Travelling Club of North America which had visited Great Britain in 1934. There were ten members on the tour. Between August 27 and September 18, 1939, they had visited Montreal, Toronto, Ann Arbor, Chicago, Washington, D. C., Baltimore, Philadelphia, New York, and Boston.

There is no doubt that America is years ahead in organization, method, and thoroughness of investigation. It appears more than probable that a certain amount of this investigation is overdone and represents a wasted effort, except that it keeps their staffs employed. On the other hand, the preoperative investigation of the gynecologic patient must be of benefit. In all, it reduces itself to a question of expense, as these hospitals are enormously costly and the nonmedical people to whom we talked complained of the cost of illness.

There was comparatively little midwifery seen, as cases will not occur according to plan, but they did not seem to err on the side of conservatism. It is impossible to compare the morbidity rates, as the standards varied. In general, their criteria are more stringent than ours, four-hourly charts being the rule rather than the exception. In operative gynecology, we were most struck by the expert manner in which vaginal hysterectomies were performed. Their operations for the cure of prolapse, where no hysterectomy was done, often seemed inadequate. While they were willing to remove the whole uterus by the vaginal route, there appeared to be a very general reluctance to perform total abdominal hysterectomy. In at least half a dozen cases the cervix was so infected that it had to be cauterized or otherwise treated from below, and then the abdomen was opened and subtotal hysterectomy performed.

WILLIAM C. HENSKE.

foam" powder type of contraception. The technique of this method is illustrated through very explicit instructions, and accompanied by demonstrations on a plaster model. There is a small charge for the material, but if the patient is completely indigent, financial aid is available for the purchase of the powder and sponge. This technique has been used by several birth control agencies with reports of varying success.

The statistical analysis of the groups is as follows:

First group (24 hypertensive patients)

Colored patients	23
White patients	1
No. using technique 6 mo. or more	10
No. in this group becoming pregnant while using technique	2
No. using technique occasionally	2
No. in this group becoming pregnant	1
No. not using technique	12
No. in this group becoming pregnant	6
No. on whom no worth-while follow-up was obtained	2
No. using material for period of time and stopping	1
No. in this group becoming pregnant	1
Total No. patients becoming pregnant	10

Second group (24 control hypertensive patients)

No. patients in group	24
Total No. patients becoming pregnant	10

Third group (56 patients with chronic diseases, etc.)

Colored patients	46
White patients	10
No. using technique 6 mo. or longer	38
No. in this group becoming pregnant while using method	9
No. using technique occasionally	4
No. in this group becoming pregnant	4
No. not using technique	10
No. in this group becoming pregnant	5
No. using material for period of time and stopping	16
No. in this group becoming pregnant	10
Total No. patients becoming pregnant	28

Totals of the first and third groups:

No. patients referred	80
Colored patients	69
White patients	11
Total No. patients becoming pregnant	38
Or 40 per cent of referrals.	
Total No. patients using method 6 mo. or longer	48
No. in this group becoming pregnant during this period	10
Or 20 plus per cent effectiveness of the method.	

In the discussion of the above analysis, it must be pointed out that the cases were not in any way selected, other than as stated. The totals represent all of the patients referred from the maternity clinic to the birth control clinic, on whom any follow-up could be obtained; a period of time slightly in excess of three years that was covered by the study. Accurate and appreciably worth-while follow-up of any of the patients was difficult but only rarely impossible. The patients in the first and second groups were or had been seriously ill, and had exhibited extensive disorders of the vasomotor and allied systems to such a degree that they were classified as pre-eclamptic, eclamptic, or hypertensive individuals.

TABLE VI. COMPARISON OF SMEARS AND CULTURES OF CERVIX AND URETHRA COMBINED

	NO.	% OF + CULT.	% OF TOTAL
Patients cultured	216		
Total cultures	1598		
Total + cultures	535		33.5
Smear Culture			
+ +	148	27.7	9.3
E* +	106	19.8	6.6
?† +	43	8.0	2.7
- +	238	44.5	14.9
+ -	4		0.25
E* -	9		0.56
?† -	19		1.19
- -	1031		64.5

*Typical extracellular diplococci in clumps.

†Typical extracellular diplococci, but no clumps

TABLE VII. COMPARISON OF SMEARS AND CULTURES

	CERVIX			URETHRA		
	NO.	% OF + CULT.	% OF TOTAL	NO.	% OF + CULT.	% OF TOTAL
Patients cultured	216			216		
Total cultures	1,656			1,675		
Total + cultures	548		33.1	405		24.2
Smear Culture						
+ +	129	23.5	7.8	33	8.1	2.0
E* +	93	17.0	5.6	50	12.3	2.7
?† +	42	7.7	2.5	42	10.4	2.5
- +	284	51.8	17.1	280	69.1	16.7
+ -	5		0.3	1		0.05
E* -	10		0.6	3		0.2
?† -	19		1.2	6		0.4
- -	1,074		64.8	1,260		75.2

*Typical extracellular diplococci in clumps.

†Typical extracellular diplococci, but no clumps.

infection. Only 8.1 per cent of the positive urethral cultures were associated with positive smears, 69.1 per cent with completely negative smears. Twenty-three and one-half per cent of the positive cervical cultures were associated with positive smears; 51.8 per cent with negative smears.

In this connection it is important to know whether both sites of infection respond to treatment equally well. Table VIII gives the incidence

TABLE VIII. INCIDENCE OF VARIATION OF CERVICAL AND URETHRAL CULTURES

	NO. OF PATIENTS	NO. OF TIMES	TIMES PER PATIENT	NO. OF DAYS
Cervix +, urethra -	32	73	2-11	7-51
Cervix -, urethra +	10	14	2- 5	7-40

of variation of cervical and urethral cultures. Forty-two patients showed one site positive and the other negative for more than two consecutive times. Usually the cervix is the most resistant site of infection, but occasionally the residual infection is found in the urethra. Smears are even less reliable here.

Special Article

MODELS, MANIKINS, AND MUSEUMS FOR OBSTETRICS AND GYNECOLOGY*

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NATURAL history is taught with striking success in three dimensions, in natural sizes, and in normal colors. Anatomy can, for the most part, only be taught adequately in actual proportions in three dimensions. Mechanisms of delivery and steps of operation can only thus be clearly visualized. Drawings and movies are makeshifts. The tortuous trip of the fetal skull through the winding pelvic tunnel, and the enforced moulding of ball into egg cannot otherwise be demonstrated. The attempt to teach students forceps extraction or podalic version except on a manikin is pedagogic malpractice. To utilize the living woman as a first step forward familiarizing the student with the finger tip findings of early pregnancy, of retroversion, or of reposition, when this can be done on a lifelike model, is not alone callous and unwarrantable, but the clinic opportunities are limited and inadequate; the tempo hurried.

Apropos of insufficiency of material, pelvic structure such as muscular and fascial planes and vessels and relations of organs will have to be taught with models as long as present conditions persist. The proportion of female cadavers available for dissection of the reproductive organs runs, I am told, to less than 5 per cent of the bodies obtained from the morgue. Moreover, these are chiefly of old women with atrophic tissues. In trying to find pelvic floors to dissect in order to make a new series of accurate and low-priced models for our obstetric-gynecologic museums, I am actually having to apply to several universities.

Most operations are on a scale such that no more than one onlooker on each side of the operator, in addition to the assistants, can observe the details. All manipulations inside the abdominal cavity or up the vaginal canal are out of sight, except with large tumors or considerable prolapse. Only cesarean section or big fibroids can be shown to a section or a class. In teaching the anatomy or the stage of the operation each student, undergraduate or postgraduate, should have in his own hands the model of the structure. One model to pass around the class can never synchronize with the words of the instructor.

All this is illustrative of the point I am trying to drive home. This is that we must have models in such number that they are not merely shelf exhibits, but hand-to-hand pieces. Therefore each must be light in weight, strong in material, and cheap in price. One of the best examples of what I mean is an actual experience from my own teaching. A sculptor who later became famous and actually wealthy, could not pay for his first masterpiece, namely, the dimpled pink model he and

*Read at a meeting of the New York Obstetrical Society, February 11, 1941, with exhibit of birth series and pelvic teaching series.

his wife created. So I gave him a receipt in full after he had made me a pelvis and a fetal skull, exactly half life size. This pair of models, cast in quantity in reinforced plaster, could be sold to my students for a quarter. They learned fontanels, flexion, rotation, and position, each with his own in his hands. This plan I am now reviving, hoping, moreover, to put both pelvis and head into a slightly flexible form, so that the pelvic cavity can be compressed to show a funnel shape, and the inlet made oval or flat or oblique, then jump back to gynecoid; and the head allow for molding by hand pressure.

Here is a second revival—again, after a half century. To teach repair of birth injuries to the pelvic floor, I provided the students with models of cheap flexible material, lifesize, showing at least two varieties of laceration, for suturing. The tear can be drawn open to demonstrate the different planes or the jagged character of the damage, the depth and distance up the posterior or lateral vaginal wall. Layer stitching is feasible. Demonstration of too shallow bite or defective apposition is facile. Gelatin and not living structure pays the penalty of mistakes and fumbling.

Of the pelvic teaching models in rubber this is the first demonstration. These models are for familiarizing the student with bimanual palpation of normal and other findings. The compressibility of the isthmus in early pregnancy cannot often be found in the outpatient department for demonstration. Here is a manual training which allows time for persistence until the eye in the finger tip gets real acuteness. It is a skill we of the last century *had* to possess, and we want the new generation of students to develop it fully again.

For instruction in placing the diaphragm in contraceptive clinics, a model is found very welcome to patients in order to demonstrate the location of the diaphragm when in proper place, both reaching behind the projecting cervix and also tucked under the bony arch in front. It shows the patient that nothing can escape upward. A second model is a vulva with the vagina of a shape to accommodate the circular pessary, and it is provided with a window in the anterior vaginal wall. This serves two purposes. All patients are taught to recognize the feel of the cervix, first without cover, and, second, after the rubber of the dome of the diaphragm is over the projection. With this model she can see her finger tip touch the cervix. Then she slips in the compressed circle, which she can watch as it either passes the cervix or stops against it. Once it is expanded in proper place, her finger palpates the covered cervix. It then crooks forward to make sure the anterior rim of the device is hooked in under the pubic arch. If her finger tip is unable to touch the protected "mouth of the womb" which is right under her eyes, she can have confidence he cannot either.

Furthermore, there are, in these days, certain patients given to asking questions. And more and more they are becoming better and better satisfied if they are given an explanation adjusted to their particular capacities. The simplest answer, whenever any demonstration is thought desirable, is of course, the diagram, preferably of life size. Where only the roundness of organs can explain the matter, then a finished type of illustration is needed. Where actual comprehension of the replacement of a retroversion, or where there is a tumor or a prolapse to be visualized, then the model, this flexible model, comes into its own. I have known an intelligent woman persuaded on the instant to have treatment or operation, because she could grasp the idea readily, when she otherwise

would have had to hark back to her mother's or grandmother's mental state—the time when, if The Doctor said so, that was all there was to it.

The "Birth Series," sculpture of the stages of labor, has already been described in the October issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, but it has never been presented as part of a medical program. Again I draw attention to the very elaborate research among the roentgenograms of six large series which were milked to get this detail. These are not the cadaver obstetrics of the picturing of the textbooks. This is life in action, life arriving, tense and not collapsed. The x-ray film now delineates soft parts. As examples of its records, delivery on the x-ray table gives us this extraordinary lift of the external os nearly out of the inlet, and this thinness of uterine wall.

Two new models that are rather complex have just been added to the series.

"Birth Prelude," the three-foot disc of the ten intrauterine months, and "Birth Relief," the ten-panel half-size group, have been pictured in the *JOURNAL* in October. My present business with all these is to reproduce them in a material which is light and not fragile, to meet the demand for travel to exhibits on the part of state health boards and maternity centers. Plaster is right for museums only.

The baby shown in the models is in two forms. One is after regaining of birth weight, of average dimensions and weight, in flexible rubber composition, eventually to be articulated. The other is the toy or doll, issued in this form in order to test the wearing qualities of various compositions of rubber by the hard usage of the playroom. The distinguished sculptor, Miss Malvina Hoffman, has visited our maternity nurseries to make this original, and as author of the book, *Sculpture Inside and Out*, has put her special knowledge, as well as her great skill, on the problem of furnishing us with a manikin, perfect for teaching as well as a beautiful example of form. The toy purposely lacks flexibility and play of joints, and the fontanels and molding quality which are being studied.

Drs. Caldwell and Moloy have cooperated with Miss Hoffman, Mr. Belskie and myself, and Dr. J. B. Truslow, in trying to work out types of pelvis. These can eventually be furnished in a rubber compound, mounted on a stand, at a price less than the bony pelvises that are usually compounds of more than one type. Dr. Moloy shows samples of types. The remarkable demonstration of passage in relation to passenger from reconstruction by stereoscopy and from molds taken from the newborn head, is a conspicuous forward step.

The Museum which every department of obstetrics and gynecology should have needs three quite different forms. One is the single specimen, which can be an actual embryo or uterus or a wax model, or a reproduction from a cancer of the breast like the beautiful series of Bulbulian from the Mayo Clinic. Second comes the multiple form, for the shelves of each school, things which every department in our line needs to refer to, especially if the specimen or growth is a little unusual, so that it cannot be readily gotten for demonstration at the time of its appearance in the course. Third, is the teaching kit, such as we have been describing, for actual handling by the student, also multiple. Here the steps of operation can be in panel form, and compact in relatively small area.

The specimen of the future will not be in glass, suspended in fluid, but bedded in transparent plastic, permanently preserved in convenient form for close inspection, and thus easily passed from hand to hand.

As to color, we find that the models for medical teaching are best in full natural color, but that those in which colleges and schools show keen interest, such as the embryology and delivery series, need show form only. Here, the terra cotta tint advised by Malvina Hoffman is acceptable, with shading or lightening for special areas or membranes.

Our craftsmanship that is busied with the intricate and delicate mechanisms of the reproductive system can thus make use of all the aids now developed in educational advances and in shop instruction and in anthropology and in museum techniques.

Hudson, F. I.: *The Midwife Problem*, Delaware State M. J. 12: 176, 1940.

To provide good health service to mothers who desire midwife service, a health department should: train, supervise, and register all midwives; provide satisfactory prenatal service for all midwife cases or see that such service is provided by other agencies, and make provision that each new accoucheuse must have certain qualifications of training and experience before formal registration.

According to the author, in 1930 there were 157 midwives in Delaware; 106 of these were colored and 51 were white. In 1940 only 76 midwives were registered; 20 of these were white, and 56 were colored.

In 1929, 19 per cent of all babies in the state were delivered by midwives. In that year the infant mortality rate was 82 per 1,000 live births. In 1939, 12 per cent of all births were delivered by midwives, and the infant mortality rate was 43 per 1,000 live births.

Much has been accomplished in Delaware by providing midwife classes at regular intervals. Good instruction in the form of demonstrations has proved the best method. Didactic lectures are practically useless, since most of the words used are out of the range of the average midwife's vocabulary.

J. P. GREENHILL.

Klumpp and Weilerstein: *Sulfapyridine—Is It a Safe Drug?* M. Ann. District of Columbia 9: 83, 1940.

Under the Food, Drug and Cosmetic Act traffic in new drugs is prohibited unless such drugs have been adequately tested, and the Secretary of Agriculture must satisfy himself that the drug is safe before permitting the application for sale to become effective. In order to do this the manufacturers were contacted, and it was learned that about 280 physicians or investigators had received consignments of the drug for experimental use before January 25, 1939. Approximately 100 were justified in expressing an opinion, and their combined experiences represent knowledge gained from more than 2,000 cases of pneumococcal pneumonia in human beings.

It was the consensus of opinion that the therapeutic use of the drug was accompanied by certain untoward effects, and these were in their general nature similar to those encountered in the use of sulfanilamide. It is significant that there was no death directly attributable to the drug in the series of cases investigated. It is seen from the table listing the toxic manifestations that nausea occurred in 36 per cent and severe vomiting in 12 per cent of the cases reported. Dizziness, cyanosis, renal symptoms, and fever occurred in the order listed.

In answering the question, "Is sulfapyridine a safe drug?" the authors say that it seems to be.

J. P. GREENHILL.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

THE SALVAGE OF FETUSES IN GRAVIDIC TOXEMIAS*

A STATISTICAL STUDY

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THIS study is the analysis of the stillbirths in toxemic patients that occurred in Philadelphia in the first fifteen months of investigation by the Stillbirth Committee under the auspices of the Obstetrical Society of Philadelphia, with Dr. Thaddeus L. Montgomery as Chairman.

Toxemia was the most frequent known cause of these stillbirths. There were 45,750 total deliveries during the period from Oct. 1, 1937, to March 31, 1939, in Philadelphia. There were 1,024 stillbirths of twenty or more weeks' gestation. Toxemia was considered as a primary factor in 137 cases, and as a contributory factor in 41 cases.

The toxemic stillbirths were studied as suggested by Dunham, Tandy and associates¹ in relation to:

1. Whether the fetal death occurred before the onset of labor,
2. The period of gestation at which stillbirth occurred,
3. The method of delivery,
4. The frequency of certain complications of pregnancy and labor associated in this study with gravidic toxemias.¹

The complications of toxemic pregnancies were studied in relation to whether the committee regarded the condition as the primary or secondary factor in the toxemic stillbirth.

Table I shows that 75.18 per cent of the toxemic stillbirths occurred in the antenatal period, while only 18.97 per cent occurred in the intranatal period, and 5.83 per cent were not recorded.

TABLE I. TIME OF FETAL DEATH IN GRAVIDIC TOXEMIA WITH RESPECT TO LABOR AND PERIOD OF GESTATION

PERIOD OF GESTATION WEEKS	ANTENATAL		INTRANATAL		NOT RECORDED	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
20 to 27	22	88.0	3	12.0	0	—
28 to 35	38	76.0	12	24.0	0	—
36 or more	43	79.63	11	20.37	0	—
Total	103	75.18	26	18.97	8	5.83

These figures compared with the general stillbirth rate as illustrated in Table II, show a greater proportion of deaths in the thirty-six or more weeks' gestation period. There is likewise an increase in percentage of antenatal deaths over that of the general stillbirth level during any time of the gestational period, but nothing

*Read at a meeting of the Obstetrical Society of Philadelphia, December 5, 1940.

TABLE II. TIME OF FETAL DEATH WITH RESPECT TO LABOR BY PERIOD OF GESTATION*
These Figures Include Stillbirths From All Causes.

WEEKS OF GESTATION	TOTAL	DIED BEFORE LABOR		DIED DURING LABOR	
		NO.	PER CENT	NO.	PER CENT
	6,367	3,713	58.32	2,654	41.68
20-27	1,084	840	77.49	244	22.51
28-35	1,756	1,298	73.92	458	26.08
36 or more	3,478	1,542	44.34	1,936	55.66
Not reported	49	33	---	16	---

*Taken from: Am. J. Public Health, p. 494, 1938.¹

to compare with the greater percentage increase during the thirty-six or more weeks' period of gestation. Of these 137 cases of primary toxemic stillbirths, 84 had received adequate prenatal care while 35 had received inadequate care. There was no record of the type of prenatal care given in 8 cases, while in 10 instances they had no prenatal care whatever.

In reviewing the 22 cases of the antenatal fetal deaths of twenty to twenty-eight weeks, I found that 6 had inadequate prenatal care, 11 had adequate care, and 3 had no prenatal care, while 2 cases had no notation on the record. The Committee classified 21 of these cases as nonpreventable, while the remaining one was classified as the patient's failure to comply with the advice of her physician.

In the group of fetuses that died antenatally between the twenty-eighth and thirty-fifth week, there were 38 cases. Twenty-seven mothers had adequate prenatal care, 7 had inadequate care, 2 had no prenatal care, and in 1 case, there was no notation whatever. Of these 38 cases, 21 fetuses were macerated, 10 were not macerated, and there was no record in 7 instances. Of the 10 fetuses that were not macerated, only 3 mothers had had analgesia and no operative interference, and these 3 cases were considered nonpreventable by the committee.

If we try to find some causative factor for the stillbirths, and review several cases of nonmacerated fetuses with a view of fetal salvage, we find:

First (No. 96) a 28-year-old white girl, primiparous, private patient, with a previous gall bladder history, who had adequate prenatal care. Her labor of eighteen hours was associated with uterine inertia. She had eclampsia at thirty-nine weeks' gestation. She had a rectal analgesia and a low forceps delivery. The fetus was not weighed but was not macerated. This mother died. Now I feel that more efforts should have been made in treating the hypertension, rather than hurrying to deliver. This case was classified as nonpreventable.

In another case (No. 695) a twenty-five-year-old, white, private, primiparous patient with adequate prenatal care died after being delivered spontaneously with no analgesia nor operative interference at the thirty-fourth week. This death was ascribed to an error in judgment on the part of the physician.

There were 3 cases where the fetus was not macerated, and after due study, were ascribed directly to the patients for their refusal to comply with the advice of the physician.

The remaining cases of this antenatal twenty-eighth- to thirty-fifth-week group were judged as nonpreventable.

In analyzing the 43 instances which occurred during the thirty-sixth week or more of gestation in antenatal toxemic stillbirths, we find:

Twenty-seven mothers had what was considered adequate prenatal care, 10 were considered inadequate; 2 had no prenatal care whatever, and no notation was made in 3 instances.

Five mothers of these 43 cases died; 2 had had adequate prenatal care and 1 had no prenatal care. The women who died left 18 living children; they were all charity cases. Four were colored and one was white.

There were 26 macerated fetuses; 14 were not macerated and there was no record in 3 instances.

Of the 3 cases where the death of the fetus occurred intranatally from the twentieth to twenty-eighth week, only one had adequate prenatal care. These were classified as nonpreventable.

Among the 12 instances of intranatal deaths at the twenty-eighth to thirty-fifth week (it is during this period that fetuses are generally heavy enough to save, unless some abnormal placental development is present), we find:

Only one case was classified as ascribable to an error in judgment on the part of the physician. Another case was classified as ascribable to the patient. The remaining supposedly nonpreventable deaths demand scrutinizing.

CASE 700.—This case occurred in a 37-year-old, white, private, hypothyroid primipara (basal metabolic rate -20) with a history of impaired renal functions and adequate prenatal care. Her labor went seventy-two to seventy-five hours after a surgical induction by rupturing the membranes. As labor progressed the fetal heart was not heard; then 2 doses of morphine sulphate and 2 doses of sodium amytal were given. After the long labor with the patient showing signs of exhaustion, the floating head was grasped with forceps through an undilated cervix under ether anesthesia, and was delivered. The length of gestation was thirty-two weeks. The fetus was not macerated and weighed 1,474 Gm. Pathologic report was birth trauma; no pathology of cord or placenta was noted.

CASE 72.—Another patient, a 38-year-old, white, private multipara had no prenatal care. She was delivered by accouchement forcé internal podalic version after the membranes had been ruptured surgically. She had a labor of eighteen hours, during which time she had 5 convulsions. Intravenous sodium amytal was used as a narcotic agent. This occurred at the thirty-second week. The fetus weighed 2,289 Gm. and was not macerated. This mother died eighteen hours after delivery.

In analyzing the 11 cases of stillbirth of gravidic toxemias during the intranatal period of thirty-six weeks' or more gestation, very enlightening information is obtained. Here are a few cases:

CASE 793.—One patient was admitted to the hospital in convulsions. She had no prenatal care, and was delivered with outlet forceps. The patient died of a ruptured heart.

CASE 513.—Another patient under private care for albuminuria, casts and hypertension, had adequate prenatal care. During a fourteen-hour labor at the fortieth week, she received castor oil, quinine, pituitrin, surgical rupture of the membranes, morphine, scopolamine, atropine, rectal ether, and paraldehyde. She was finally delivered by the second set of forceps.

Another patient having symptoms of toxemia, during the last two months had received so-called adequate prenatal care, was allowed to have a labor of sixty-eight hours. During the labor she received castor oil, pituitary extract, morphine, scopolamine, Gwathmey's rectal ether, and magnesium sulphate. She was finally delivered by low forceps at her fortieth week of a fetus weighing 3,104 Gm. This patient died.

CASE 115H.—Another patient with a history of diabetes, hypertension, obesity, and having inadequate prenatal care, was allowed to deliver spontaneously at home in the thirty-sixth week of a very large strangulated baby which was not weighed. This is a glaring example of the need of education not only of the laity, but of some physicians who undertake the responsibility of delivering at home.

Table III shows the infrequency of the operative procedures associated with this complication of pregnancy and especially the percentage of intranatal deaths that are associated with operative interference.

There were 4 cases of cesarean section where the fetus died before delivery. Three were performed in the twenty- to twenty-eight-week group. The fourth (No. 46) was performed at the fortieth week in a forty-year-old white, charity multipara who had had two previous stillbirths. She had had adequate prenatal care. Hysterotomy was done when eye changes were noted and a nonmacerated fetus, weighing 1,502 Gm., was delivered. This was classified as being nonpreventable.

This table shows but two instances where low forceps and midpelvic forceps applications were performed and intranatal deaths recorded. There were two instances of breech extraction performed during toxemic labor, resulting in stillbirths. Version and extraction were done on only one occasion. There were no instances of cesarean section during this period of investigation which resulted in an intranatal stillbirth.

Primary toxemic stillbirths, totaling 137 cases in the first 1,024 stillbirths, were complicated by twin births in three instances. Of these 3, one went to twenty-nine weeks' gestation with adequate prenatal care and was delivered spontaneously of macerated fetuses. Another had thyroid disease complicating the toxemia. She was given adequate prenatal care but was allowed to progress until the thirty-eighth week before medical and surgical inductions were done. In this case, the first fetus was a breech, delivered spontaneously; while the second fetus (a cephalic presentation) was alive when spontaneously delivered. The third set of twins was delivered spontaneously at the thirty-ninth week by a patient with a history of mild toxemia. Death of the fetuses resulted from inadequate prenatal care, either due to the patient herself or to improper guidance by the physician. These fetuses weighed 2,428 and 3,175 Gm. According to the committee, this was classified as nonpreventable.

TABLE III. TIME OF FETAL DEATH WITH RESPECT TO TYPE OF DELIVERY

TYPE OF DELIVERY	ANTENATAL DEATHS		INTRANATAL DEATHS	
	NO.	PER CENT	NO.	PER CENT
Spontaneous	90	65.69	18	13.13
Low forceps	7	5.10	2	1.45
Midforceps	1	0.72	2	1.45
Cesarean section	4	2.91	0	—
Breech extraction	6	4.36	2	1.45
Version and extraction	4	2.91	1	0.72

Table IV shows that only in six instances was the fetal death due to birth injuries as noted on the reporting charts, and of these only two were classified as nonpreventable.

Prolapsed cord was noted twice; placental infarcts and necrosis were a contributory factor in three cases, and these were all considered as nonpreventable by the Committee.

The case of syphilis complicating toxemia was classified as nonpreventable.

It is interesting to note that placenta previa, a condition obviously nonpreventable and admittedly one in which fetal death is likely to occur, took place only twice in this group of toxemic patients.

There were 92 cases of premature placental separation during the period of study, of which 27 cases occurred in toxemia patients. Here one is absolutely and immediately confronted with the need for further study of the placenta and its relation to gravidic toxemias. There was no question of the management of any of these cases, as they were classified as nonpreventable. I feel that some of the fetuses could have been saved if we knew more of the placenta, cord, and envelopes and their relationship to this complication of pregnancy with toxemia.

Of these 27 cases of premature separation complicating labor, the fetus died antenatally in 16 and intranatally in 8 instances. There was no notation in 3 cases. This complication occurred as early as the twenty-seventh and as late as the fortieth week. There were 9 instances where hysterotomy was done; 12 were delivered spontaneously; there was one breech decomposition; one podalic version; and one case where aftercoming head forceps were used. There was one midforceps application and two low forceps applications, one of which was complicated by impacted shoulders. Of these placental separations, if the patients were immediately hospitalized and studied, although condition is more difficult to control, some reduction may have been effected.

Another factor to be seriously studied is the problem of prematurity and immaturity. It was noted that the weights of the fetuses in the various periods of gestation varied greatly in each group. Table V suggests the possibility of the co-existence of *both prematurity and immaturity*. While the rate of infantile mortality is not difficult to establish, it is quite another matter to determine the rate of immature babies. While the term immature suggests an entirely different condition from that which is indicated by the term premature, the two have often been used synonymously to express the state of debility of the newborn infant due to an incomplete development of the organism.

TABLE V. THE WEIGHTS OF FETUSES OF PRIMARY TOXEMIC STILLBIRTHS

WEEKS OF GESTATION	NOT RECORDED	- TO 400	400 TO 1,000	1,000 TO 1,500	1,500 TO 2,500	2,500 TO 4,500
20-22	2	1	1	0	0	0
22-28	10	0	12	4	3	1
28-37	16	0	6	10	21	10
37-43	6	0	0	0	7	22
Not recorded	4	0	0	0	0	0

Toxicosis is one of the most important causes of premature births, being outnumbered possibly only by twin pregnancies. Of course, syphilis and polyhydramnios are also important factors. There is no doubt that children born of women suffering from eclampsia, grave hypertension, and albuminuria show a greatly retarded development. When comparing the children of eclamptic patients with children delivered during the same gestation period, we find that they continue to present the fetal characteristics with a meager chest development that contrasts with the less relative size of the head, even though it remains dominantly large, and especially the abdomen with its absence of the panniculus adiposus.

If we consider these neonatal births simply as weaklings and later capable of having a normal development, we should equally remember the percentage that die in the first few days or weeks of life, as compared with births of nontoxic mothers in the same gestation period.

This paper would not be complete without calling to attention the relationship of the type of operative delivery, the anesthetic agents used, the management of the toxic patient immediately before the procedure, upon the immature, premature, and toxic fetus. Schreiber,² in his study of apnea of the newborn and associated cerebral injury, shows the effect of anesthesia, analgesia, oxytocics, operative, normal birth trauma on the respiratory center with a resultant cerebral anoxemia with or without irreparable brain damage on an apparently healthy full-developed fetus. If this is so, what would be the effect of all these factors on a fetus that is already handicapped with the toxic factor superimposed on a premature immature fetus?

Apnea is commonly found in a higher percentage in toxic babies born alive, but when the mother has been given analgesic and anesthetic agents over and above the pharmacologic doses recommended (whether a necessity or not) the dose may be enough to spell the difference between a live or dead fetus.

My personal opinion is that in increasing the salvage of fetuses of toxic mothers, we will be increasing at the same time the neonatal death rate, but that this increase will probably only be about one-third or one-half of the number of fetuses saved.

The complexity of the data-examined documents implies how unpropitious are the repercussions of the gravidic toxemias.

COMMENT

There was an increase of the number of toxic stillbirths antenatally over the general stillbirth rate, and more especially after the thirty-sixth week. This brings into bold relief the absolute necessity for adequate *intelligent* prenatal care.

The average age of all these toxic patients was 28.41 years.

In review of the 6 cases of birth trauma associated with toxemia, it was interesting to find that the average age of these patients was 35.6 years. Four of these were multiparas and 2 were primiparas.

I feel that hysterotomy has a very limited place in the treatment of toxemia. Excepting for actual indications, such as complicating hemorrhage, disproportion, abnormal presentation, etc., the following conditions should be fulfilled before considering cesarean section:

1. Pregnancy should be over twenty-eight weeks.
2. Evidence of fetal life.
3. Lapse of several hours from the time of administration of narcotics and analgesics.

SUMMARY

1. Cultures have been used routinely to determine the cure of gonococcal infection in women in various types of therapy.

2. Cultures have been found to be reliable and far superior to smears even when (a) Culture materials were not plated for two or three hours after they had been taken; (b) Plates were not incubated for four to five hours after they had been inoculated; (c) Plates were transported from the clinic to the laboratory (thirty to forty-five minutes) in all kinds of weather without special precautionary measures.

3. Cervical smears were more reliable than urethral smears, but even with them, over 50 per cent of the positive cultures had corresponding negative smears.

4. In the majority of cases both cervical and urethral sites of infection cleared simultaneously. In residual infections the cervix was more frequently the resistant site.

5. Tetramethyl p-phenyldiamine hydrochloride is preferable to the dimethyl compound for the oxydase test.

Acknowledgment.—The authors wish to express their appreciation for the cooperation of Drs. S. Charles Kasdon, Jack Kight, Robert G. Greene, and Lewis L. Hall of the Chicago Lying-in Hospital, who assisted in the collection of culture materials and in the examination of slides.

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- (1) *McLeod, J. W., Coates, J. C., Hapgood, F. C., Priestley, D. P., and Wheatley, B.*: J. Path. & Bact. 39: 221, 1934. (2) *Carpenter, C. M., Leahy, A. D., and Wilson, K. M.*: Am. J. Syph., Gonorr. & Ven. Dis. 22: 55, 1938. *Leahy, A. D., and Carpenter, C. M.*: Ibid. 20: 347, 1936. (3) *Malcom, M. M., and Dolman, C. E.*: Canad. Pub. Health J. 30: 252, 1939.

CLINICAL EXPERIENCE IN THE TREATMENT OF PELVIC INFLAMMATORY DISEASE WITH INTRADERMAL INJECTIONS OF BACILLUS COLI VACCINE

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(From the Department of Gynecology of Wayne University and Detroit Receiving Hospital)

THIS paper presents the clinical result obtained in the ambulatory treatment of pelvic inflammatory disease of venereal and puerperal etiology following the intradermal administrations of a suspension of *B. coli*. The intradermal method of administration was found to be easier to execute, less uncomfortable and more safe than either the intramuscular administration of "boiled milk" or the intravenous administration of typhoid vaccine. Yates and Davidow reported over 3,000 intramuscular injections of boiled milk without the occurrence of an abscess, but I have encountered four such instances, two of which patients were hospitalized for over two months. Obviously, intravenous shock therapy cannot be used in ambulatory patients.

DISCUSSION

DR. THADDEUS L. MONTGOMERY.—I am not so optimistic as Dr. Dienna in expecting an early reduction in the fetal mortality from toxemia of pregnancy. I am willing to acknowledge, however, that many of these cases are mismanaged and that more could have been done to further the interest of both mother and child. The handling of such cases and the bringing about of a better result in the mother and child require a high degree of obstetric judgment and oftentimes depend upon the combined opinion of the medical clinician, the ophthalmologist, and the obstetrician, all of whom can make their contribution to diagnosis.

As regards the role played by the placenta and particularly the frequency with which certain necrotic lesions or infarcts are noted in the presence of toxemia of pregnancy, I believe, for many reasons, that the hemorrhagic and necrotic areas which are observed in the placenta of nephritic and toxemic patients are a result of the disease and not the cause of it.

DR. DIENNA (closing).—I do not believe very much can be gleaned from a complete post-mortem examination of an extremely macerated fetus. However, in the case of a nonmacerated toxic fetus, we might learn a great deal from a complete post-mortem examination.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF JANUARY 14, 1941

The following papers were presented:

Two Unusual Cases of Chorioepithelioma. Dr. I. C. Rubin. (For original article, see page 1063.)

Chorioncarcinoma With Clinical, Hormonal and Pathological Findings. Drs. William P. Healy and John A. Kelly. (By invitation.) (To appear in a later issue.)

MEETING OF FEBRUARY 11, 1941

The following papers were presented:

Models, Manikins, and Museums for Obstetrics and Gynecology. Dr. Robert L. Dickinson. (For original article, see page 1075.)

A Comparison of the Classical and Lower Segment Cesarean Section. Dr. George H. Ryder. (For original article, see page 1029.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF DECEMBER 5, 1940

The following papers were presented:

The Salvage of Fetuses in Gravidic Toxemias. Dr. Nicholas P. A. Dienna. (For original article, see page 1079.)

Ovarian Transplantation. (Moving Picture.) Drs. Michael J. Bennett and Newlin F. Paxson.

4. Active treatment of *toxemia*, not simply hypertension, for a reasonable length of time in a hospital.
5. Obstetric consultation.

A glance at the case reports definitely shows the importance of education of patients and education of general practitioners who do obstetrics in not waiting too long before seeking obstetric advice in the management of toxemic patients. The importance of actively treating the toxemia, not simply hypertension, and, if no improvement is noted, or if the toxemia increases in severity, the advisability of induction of labor is certainly borne out. Labor then should be induced medically, and only surgically if necessary, during a period when the fetus is free from possible effects of narcotic agents.

A study of the cases of intranatal stillbirths showed that as a rule:

1. Interference came too late.
2. Effect of narcotics, analgesics, and anesthetics was not too seriously considered.

During the same period, there were 92 cases of premature separation, 27 of which were associated with toxemia.

There were so few autopsies done on these fetuses that deductions could not be drawn.

SUMMARY

1. An analysis of 137 toxemic stillbirths complicating the first 1,024 cases of stillbirth studied by the Philadelphia Committee from Oct. 1, 1937, to March 31, 1939 are reported. During that period, there were 45,750 total deliveries.

2. Evidence is given showing an increase in the antenatal deaths of the toxemic fetuses during any time of the gestational period as compared with the general stillbirth level.

3. The greatest increase of the percentage of antenatal deaths of the toxemic fetuses occurred in the thirty-six or more weeks' gestation period.

4. There are still a great number of patients with inadequate prenatal care, notwithstanding the education in this respect.

5. There is lack of proper guidance of the toxemic labor.

6. Evidence is presented showing the haste of operative interference before careful study and management of the toxemic mother.

7. The greater vulnerability of the premature and immature toxemic fetus to drugs and interference is discussed.

8. A plea for complete study of the placenta, cord, and envelopes in all stillbirths is presented.

CONCLUSIONS

1. Toxemic patients must be carefully studied and closely watched.

2. There should be careful management of the toxemic labor with special attention to noninterference unless the mother has first been treated; and the use of analgesic and anesthetics should be limited to the very minimum.

3. Inadvisability of cesarean section before the twenty-eighth week unless all other methods fail should be considered.

4. Labor should be induced as soon as the toxemic mother with alarming symptoms (not simply hypertension) does not respond to treatment.

5. Unusually strict and constant supervision of the fetus after delivery should be followed.

REFERENCES

- (1) *Dunham, et al.*: Am. J. Pub. Health 28: 491, 1938. (2) *Schreiber, Frederick*: J. A. M. A. 3: 1263, 1938.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Labor

Basden, Margaret: A Maternity Hospital at the Home Front, *Brit. M. J.* 2: 453, 1940.

The author describes the effect of war on the routine of a Maternity Hospital at the home front. She discusses the facilities afforded the patients for their protection during air raids, the routine by which these facilities are taken advantage of, the modifications required in the treatment of post-partum and postoperative cases, and the apparent and undetermined results of such modifications in treatment.

Post-partum patients are allowed up a few minutes the day the baby is born and patients having abdominal operations on the fifth postoperative day. Subsequent activity is increased daily.

The favorable results noted include the creation of a carefree and happy atmosphere among the patients, a decrease in morbidity, better uterine involution, considerably less venous thrombosis, and stronger and healthier patients on discharge. The author warns that the early adoption of the erect position may increase the tendency to prolapse and too short a stay in bed after operation or confinement may lead to neurasthenia.

FRED L. ADAIR AND W. H. PHILLIPS.

Thomas, Rufus C.: 3,144 Consecutive Deliveries Without a Maternal Death Due to Pregnancy, *Brit. M. J.* 1: 562, 1940.

Between Jan. 3, 1938, and June 4, 1939, the Corydon Obstetric Service has conducted 3,144 consecutive deliveries without a maternal death attributable to pregnancy. One mother died of pneumococcal pneumonia on the day of delivery which began seven days before. These cases are drawn from all possible sources.

Complete antenatal, natal, and postnatal care is available to the patients and the services of the Borough obstetrician are available to all medical practitioners in the area.

All prenatal patients with an elevated blood pressure, with or without albuminuria, were hospitalized for observation and study. If at the thirty-second-week examination the patient was found to have a breech presentation, external version was attempted. If unsuccessful, the patient was hospitalized, placed in a Trendelenburg position for one to two hours and another effort made. About 75 per cent were successfully converted.

The lower segment operation was done in 49 per cent of 74 cesarean sections, and 59 of these were done under spinal anesthesia.

The stillbirth rate was 28.9 per 1,000 total births, and infant death rate was 13.9 per 1,000 livebirths for the series.

FRED L. ADAIR AND JOHN R. KIGHT.

Kosakae, J., and Okai, K.: The Onset of Labor Pains by Follicular Hormone Is Induced Through the Posterior Lobe of the Pituitary Body, *Jap. J. Obst. & Gynec.* 23: 172, 1940.

It was previously shown that follicular hormone may successfully be used to stimulate contractions of the uterus. The authors induced labor by means of placental substance. They believe the mechanism of the production of labor pains

MEETING OF JANUARY 2, 1941

The following papers were presented:

Spontaneous Painless Parturition in Pregnancy Associated With Transverse Myelitis. Dr. J. Stanley Cohen (by invitation).

Hydatidiform Mole Followed by Chorionepithelioma. Dr. Edward F. McLaughlin.

The Contractile Response of the Pregnant Human Uterus to Posterior Pituitary Extract. Dr. Douglas P. Murphy. (To appear in a later issue.)

Ovarian Hemorrhage. Drs. Mario A. Castallo and Louis Feo.

MEETING OF FEBRUARY 6, 1941

The following paper was presented:

Tumors of the Reproductive System in the Rabbit With Especial Reference to Etiological Relationships and to the Development of Autonomy. Dr. Harry S. N. Greene (by invitation).

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 3, 1941

The following papers were presented:

Supravescical Extraperitoneal Cesarean Section (Waters' Operation). Drs. J. R. Eisaman and B. R. Austin (by invitation). (For original article, see page 1060.)

Purpura Hemorrhagica Complicating Pregnancy. Dr. David O'Laughlin.

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 7, 1941

The following papers were presented:

The Immediate Treatment of Obstetric Hemorrhage and Shock. Dr. Charles A. Gordon. (For original article, see page 1056.)

Studies in Pelvic Iontophoresis of a Choline Compound. Drs. Charles A. Gordon and Alexander H. Rosenthal. (For original article, see page 1043.)

A Method for Preventing or Diminishing Peritonitis From Leakage After Intestinal Resection or Perforation. Dr. Harry Koster.

Sharkey, John A.: Should Solution of Posterior Pituitary Be Used in the First and Second Stages of Labor? *J. A. M. A.* 115: 1315, 1940.

The author emphasizes the fact that solution of posterior pituitary should not be used in normal labor, and again points out the dangers to child and mother, chief of which are intracranial hemorrhage and injury to the musculature of the uterus resulting from tetanic contractions. In cases of uterine inertia the solution of posterior pituitary should be limited to certain cases of true primary inertia and he enumerates several conditions in which it should not be used. Posterior pituitary is certainly not indicated in secondary inertia. The author feels that its use is contraindicated in toxemia of pregnancy, placenta previa, and heart disease, but in skilled hands it can occasionally be advantageously employed in abruptio placentae.

WILLIAM BERMAN.

Kühnel, P.: Further Experience With Scalp Forceps Traction in the Treatment of Uterine Atony, *Acta. obst. et gynec. Scandinav.* 20: 139, 1940.

The author reports 11 additional cases of protracted labor with secondary atony treated by means of scalp forceps traction. The good results obtained lead him to recommend strongly the use of this method in suitable cases of uterine atony.

J. P. GREENHILL.

Dawson, J. Bernhard: The Occipito-Posterior Position, *Brit. M. J.* 1: 612, 1940.

A review of 3,700 deliveries revealed 415 cases of occipito-posterior positions, not including those better designated as occipito-lateral or transverse. Of these, 30 per cent delivered face to pubes naturally or with forceps, 50 per cent rotated and delivered naturally or with forceps, and 20 per cent required manual or forceps rotation.

That the size of the infant is not a factor in the persistence of occipito-posterior position was shown by the small difference in infant weights in the above 3 groups. Parity apparently played little part in the etiology of posterior positions, and a predominance of multiparas in the first and second groups does not support the contention that laxity of pelvic tissues may adversely influence anterior rotation. An equal number of primiparas and multiparas required rotation, suggesting a common factor, such as the pelvic type, but this was disproved by a lack of repeated occipito-posterior positions in multiparas.

Infant mortality of the posterior positions compared favorably with that of the entire group, being slightly better for infants that rotated spontaneously.

Average duration of labor was increased in primiparas, but showed little difference in multiparas.

The author's treatment consists of noninterference until the mother's or baby's condition necessitates delivery, or careful examination reveals a failure in the progress of labor. His method of manual rotation is described.

FRED L. ADAIR AND JOHN R. KIGHT.

Guerriero, W. F., Arnell, R. E., and Irwin, J. B.: Pelvicephalography: An Analysis of 503 Selected Cases, *South. M. J.* 33: 840, 1940.

In order to evaluate the accuracy of the Ball method of pelvicephalography, a clinical and radiologic study was made. It was based upon 503 cases of patients with prolonged labors, evident or suspected fetopelvic disproportion, abnormalities of the bony pelvis, and a number of normal patients selected from a series of over 6,000 deliveries. Other causes of dystocia were eliminated. There were 191 white and 312 colored patients; 362 of the presentations were vertex and 38 were breech.

Roentgen pelvimetry eliminates the ever present, variable factor of personal equation and assures accuracy in the determination of all the pelvic diameters. In addition to pelvic measurements, such other information of clinical value may be ascertained, as details of pelvic architecture, cephalopelvic proportions, the pos-

is the acceleration of the secretion of oxytocin, because follicular hormone does not act directly upon the uterus. The authors proved that there was an increase in the oxytocin content of the cerebrospinal fluid in animals after the injection of placental substances. Contractions of the uterus were obtained only after a certain concentration of oxytocin was observed in the cerebrospinal fluid.

J. P. GREENHILL.

Spiller, V.: *An Inquiry Into the Hour of Birth*, Brit. M. J. 1: 435, 1940.

Of 2,225 patients delivered per vaginam during the years 1934 to 1937 at the Royal Free Hospital, 5.25 per cent more were delivered at night, between 8 P.M. and 8 A.M. than during the day.

FRED L. ADAIR AND JOHN R. NIGHT.

Olivella, J. R.: *Hour and Month of Births*, Rev. cubana de obst. y ginec. 2: 45, 1940.

Olivella studied the records of more than 22,000 strictly spontaneous births. In cases of multiple births the time of expulsion of the first infant only was noted. Of the above number, 10,590 infants were born between 6 A.M. and 6 P.M.; 11,438 between 6 P.M. and 6 A.M. No great consistency was shown from year to year in the hour of most or least births, but over a five-year period 1,039 infants were born at 1 A.M. and 2 A.M. each, and the hour of least births was 5 P.M., with 777. The author discusses the possible effects of solar influences in initiating labor during the day.

R. J. WEISSMAN.

Paton, D. M.: *Studies in Obstetric Analgesia*, South. M. J. 33: 626, 1940.

This study was based upon the use of several analgesic agents in two series of patients totaling 958 cases. Of these, 610 received some type of analgesia. The primary aim in the management of these labors was to secure first stage analgesia with amnesia. Medication was given as early in labor as it was safe to do without the risk of checking its progress. A variable degree of restlessness occurred with all the analgesics. It was either absent or only slight in 63 per cent of the patients who were given sodium amyl-beta-bromallyl barbiturate (sigmodal). The complementary use of small doses (gr. $\frac{1}{6}$) of "pantopon" with pentobarbital and hyoscine combinations appreciably decreased this undesirable side effect. This drug was omitted when the progress of labor was very rapid and delivery seemed imminent. Effective amnesia was obtained in 80 to 85 per cent of the patients to whom pentobarbital-hyoscine-pantopon and pentobarbital-hyoscine were given; in 65 per cent of the morphine-hyoscine group, and in 64 per cent of those patients in whom sodium amyl-beta-bromallyl barbiturate (sigmodal) was used. Rectal ether is stressed as a valuable analgesic agent for use late in the first stage of labor, or even in the second stage when it might be unsafe to employ other drugs. There was no increased incidence of operative delivery.

Two maternal deaths occurred, neither of which was attributed to the use of analgesic drugs. One very toxic patient died of shock resulting from premature placental separation; she had received 6 grains of sodium iso-amyl-ethyl barbiturate (sodium amytal). The second patient had a retained placenta and death from septicemia occurred two weeks post partum. Early in labor "sigmodal" was given and twelve hours later, pentobarbital and hyoscine.

A total of 15 fetal deaths occurred. Of the two in the first series, one infant was born of an eclamptic mother. Both eclamptic patients received "average effective morphine-hyoscine narcosis." In the second series, there was sufficient cause for the deaths, exclusive of the use of any of the drugs. One of the conclusions of the author is that, "the danger to the baby is negligible in the hands of one trained in the use of analgesics."

ARNOLD GOLDBERGER.

with the least amount of shock is indicated. Three contraindications to the performance of craniotomy are also indications for abdominal delivery: (1) a true conjugate of less than 5.5 cm.; (2) tumor blocking the pelvis; (3) a fibrous or carcinomatous cervix. A patient who has had one craniotomy should subsequently be delivered in some place where better obstetric facilities are available.

In a ten-year period, during which there were 12,292 deliveries, 29 craniotomies were performed, an incidence of 0.235 per cent. Of these, 12 of the patients had received prenatal supervision in the hospital clinic, and 17 patients were referred from elsewhere. The specific indications for the craniotomies in the series numbered ten. Twenty-four of the infants were dead when the operation was performed; 4 babies were hydrocephalic. The duration of the longest labor was approximately 98 hours. In the majority of instances there was a history of membranes having been ruptured for many hours; the longest periods were 178 hours and 144 hours.

There were 7 maternal deaths, a mortality rate of 24.1 per cent. Six of the deaths occurred in nonclinic patients, and in 5 of them there were vaginal examinations with attempts at delivery in the home. The patients were in poor or critical condition when the operation was performed, and, with the single exception of a patient whose pregnancy was interrupted at five months for medical indications, they had been in labor from 40 to 74 hours. The one clinic patient had a hydrocephalic baby; she was examined vaginally in the hospital and had a bag induction of labor. There was no autopsy and death was ascribed to embolism or surgical shock.

ARNOLD GOLDBERGER.

Item

Postgraduate Course

The Illinois State Department of Public Health and the Children's Bureau, U. S. Department of Labor are sponsoring ten four weeks' courses in obstetrics at the Chicago Lying-in Hospital during the fiscal year 1941-1942. Only a limited number of physicians will be accepted for each course. The only cost to the individual is for room and board and \$25.00 (\$10.00 of which is refunded at the completion of the course). Applications and inquiries should be addressed to: Postgraduate Course, Department of Obstetrics and Gynecology, 5848 Drexel Avenue, Chicago, Illinois.

Books Received

HOLT'S DISEASES OF INFANCY AND CHILDHOOD. By the late L. Emmett Holt and John Howland. Revised by L. Emmett Holt, Jr., M.D., Associate Professor of Pediatrics, Johns Hopkins University, etc., and Rustin McIntosh, M.D., Carpentier Professor of Pediatrics, Columbia University, New York, etc. Eleventh edition, 262 figures, 1421 pages. D. Appleton-Century Company, New York, 1940.

THE MERCK MANUAL. Therapeutics and Materia Medica. Seventh edition, 1436 pages. Merck & Co., Inc., Rahway, N. J., 1940.

MACLEOD'S PHYSIOLOGY IN MODERN MEDICINE. Edited by Philip Bard, Professor of Physiology, Johns Hopkins University School of Medicine. Ninth edition, 387 figures, 1256 pages. The C. V. Mosby Co., St. Louis, 1941.

MODERN DRUG ENCYCLOPEDIA. Therapeutic Guide. By Jacob Gutman, M.D., Phar.D., F.A.C.P., Director, Brooklyn Diagnostic Institute, etc. Second edition, 1644 pages. Published by New Modern Drugs, New York City, 1941.

A FAMILY DOCTOR'S NOTEBOOK. By I. J. Wolf, M.D., Professor of Medicine, Emerit. University of Kansas School of Medicine. Fortuny's, New York, N. Y., 1941.

sible occurrence of intrauterine fetal death, malformations and multiple gestation. This method of pelvimetry requires an anteroposterior and a lateral view of the pelvis. The former reveals the contour of the inlet, the basis for the Thoms classification of pelvic type, which was employed in this analysis, as well as the outline of the ischial spines. The prominence of these spines as a factor in dystocia seems to depend upon the adequacy of the transverse diameter of the midplane, and the adequacy of the posterior half of the midpelvis ("compensation of the posterior pelvis"). When these factors are ample, prominence of the spines per se is not likely to cause dystocia. From the lateral view may be obtained information concerning the lumbar spine, the contour and position of the sacrum, the sacrococcygeal articulation and the hip joint. The most frequent pelvic type was the brachypellic, with an incidence of 48.1 per cent; the mesapellic type was next and occurred in 32.9 per cent. On a racial basis these two types predominate. In the colored patients, these appeared in the same order as for the entire series; among the white patients the order was reversed.

The Ball method of pelvicephalography is based upon volumetric comparisons of the fetal head at the pelvic inlet and at the midplane. By Ball's mechanical calculator, a correction is made for magnification, and then the fetal head circumference and pelvic diameters are determined. These data make possible a calculation of volume capacity of the pelvis and of the fetal head, from which it is possible to make cephalopelvic volume comparisons. Dystocia at the inlet is predicted if the volume of the head exceeds the volume capacity of the inlet by more than 150 milliliters; and miplane dystocia when the fetal head volume exceeds the volume capacity of the midplane by more than 250 milliliters. The authors adopted their own standard of 200 milliliters for the criterion of inlet dystocia. They stress the fact that dystocia often results from a combination of borderline inlet volume relations with a midplane, and emphasize the importance of a consideration of the posterior sagittal dimension in midplane pelvicephalometry. The value of this procedure was decreased in breech presentations, where discrepancies between the x-ray findings and the clinical course occurred.

Roentgen study of the pelvis and cephalopelvic relations by the Ball method provides data which may be of prognostic significance. It should be considered as a laboratory aid, and the results interpreted in the light of clinical judgment and experience.

ARNOLD GOLDBERGER.

Frawley, M. D'Arcy: *The Treatment of Disproportions*, *Canad. M. A. J.* 44: 38, 1941.

The author reports the occurrence of 53 instances of disproportion in 1,000 consecutive deliveries. Its presence was anticipated in two-thirds of the cases. Elective cesarean section was performed in 4 instances. The remaining 49 were subjected to a test of labor. Of them 9 delivered spontaneously, 33 following forceps (1 high forceps), 2 were delivered by version and extractions, and 4 were finally delivered by low segment cesarean section. Craniotomy was performed on one dead infant. There were 2 maternal deaths, both due to infection and 3 infants' deaths due to asphyxia.

CARL P. HUBER.

Long, J. P., Jr., and Stabnick, J. S.: *Craniotomy*, *South. M. J.* 33: 1073, 1940.

There is evidence that craniotomy was performed in antiquity, and that in 3000 B.C. the operation was done in certain difficult labors by priests. The instruments and methods devised by Paré, Levret, Smellie, and Baudelocque are still largely used today with some slight modifications.

The principal indications for the procedure are: (1) where a positive diagnosis of hydrocephalus or other monster formation has been made; (2) in breech presentations when the infant is dead and slight cephalopelvic disproportion exists, or when the head is impacted and the chances of obtaining a live baby are very slight; (3) whenever the baby is dead and cannot be easily delivered by forceps or version; (4) in certain instances where the mother is in a critical condition and a rapid delivery

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*January, pp. 1-178; February, pp. 179-354; March, pp. 355-546; April, pp. 547-732; May, pp. 733-914; June, pp. 915-1110.

This report represents the first group of 172 cases in our investigation, which began in July, 1933. There was no selection of patients and no other medical treatment was administered except placebos for the control of severe pain and douches for cleanliness.

PREPARATION OF THE VACCINE

The first vaccine used was a suspension of *Staphylococcus aureus*, which was discarded because of the relatively large amounts required to produce a reaction. The colon bacillus was then selected, and a vaccine containing one-half billion organisms per cubic centimeter was used. This concentration was gradually increased until our present vaccine, in use during the last four years, contains three billion organisms per cubic centimeter.

Mrs. Edith Hamilton, chief bacteriologist, prepared these vaccines in the laboratories of Receiving Hospital. A culture was obtained from a fresh stool specimen, grown on agar and put up in normal saline containing 0.5 of 1 per cent of tricresol. This material was used when negative cultures were obtained on three successive days and in the absence of spores. Specimens of this material standing at room temperature were found sufficiently potent at the end of sixteen and thirty months, respectively.

Our one experience in sterilizing with heat resulted in the destruction of the active agent and our clinical results approached zero.

It is an interesting observation that the most commonly used vaccines for the production of foreign protein shock therapy contain the bacillary form of organisms, i.e., typhoid, colon, lactic acid.

METHOD OF ADMINISTRATION

The technique of administration was the same as that employed in the "Schick test," followed by gentle massage. A needle of 22 or 24 gauge was of distinct advantage.

The injections were made at least six inches apart to avoid the necrosis that follows Arthus' phenomenon. The thigh was the site of preference because small areas of local induration and discoloration may be present for as long as six weeks.

An arbitrary number of six injections was selected to constitute "a series" or course of treatment. The injections were given twice weekly if the reactions were not too severe, otherwise, once weekly. Two weeks after a series was completed a re-examination was done, and a decision was made as to whether additional treatment or a change of treatment was advisable.

The initial injection was one-fourth cubic centimeter. Each successive dose was increased by one-fourth cubic centimeter up to a maximum of one cubic centimeter.

Occasionally when the local reaction was too severe or too small the initial amounts were varied so that a local reaction of several days' duration was obtained which was followed by a local area of induration at the site of the needle puncture.

EFFECTS OF ADMINISTRATION

The effects of the administration of the *B. coli* suspension have been similar to those obtained after the administration of other forms of so-called shock therapy, except that in the majority of cases they have been less severe.

The local effect was swelling, redness, pain, and temperature. A few days after the administration of the vaccine a small area of induration appeared at the site of injection and would frequently remain for several weeks. Occasionally subsequent injections brought about a reoccurrence of initial symptoms at the site of previous administrations. In a few

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cases small areas of necrosis occurred when successive injections were injudiciously placed too close together.

The effect upon the pelvic pathology was also similar to other forms of shock therapy. Exaggeration of the pelvic symptoms might occur followed by improvement of the pain. In the majority of cases the pelvic pain was relieved to a great extent following three or four injections. The vaginal discharge also lessened. An interesting situation occurred in a number of cases which puzzled us in the beginning of our investigation. Following a series of treatments and the two weeks' waiting period, the women would come in for the check-up examination complaining bitterly there had been no relief of their pain and presumably of their illness. Abdominal and vaginal examinations revealed a practically normal pelvis. The uterus was freely movable without pain; there were no adnexal masses or areas of induration of the broad ligaments; there was little or no vaginal discharge. We have attempted to explain this situation by suggesting that the original inflammatory process had not subsided about, or in, the sensory nerves as rapidly as it had subsided in the other tissues. Additional therapy was found to be not necessary. In private practice these cases have been helped by heat induced by the high frequency current.

The general effects of the vaccine were similar to those experienced in other forms of shock therapy. Malaise, dizziness, headache, nausea, vomiting, diarrhea, chills, fever, etc., might appear in any combination and intensity in from three to twelve hours. These reactions would last for several hours to a day or two. The changes in temperature and pulse rate taken at two-hourly intervals following intradermal administrations were followed in fifty instances. The average temperature rise was 1.8° F., which lasted on an average of 4.1 hours. Coincidentally, the average rise in pulse rate was 17.9 beats per minute.

CLINICAL STATISTICS

In this series the white patients numbered 76, the blacks, 96.

Eighty-eight patients had been hospitalized from two to seven days prior to discharge to the outpatient department for medical therapy.

The follow-up periods averaged 11.4 months following the last treatment.

TABLE I. SERIES OF VACCINE GIVEN AND MONTHS OF TREATMENT GIVEN

NUMBER OF SERIES OF SIX INJECTIONS	CASES	NUMBER OF MONTHS OF TREATMENT	CASES
Less than one	8	Less than one	3
One	122	One	118
Two	35	Two	27
Three	5	Three	10
Four	1	Four	3
Five	1	Five	2
		Six	3
		Seven	3
		Nine	1
		Fifteen	1
		Forty-two	1
Total	172	Total	172

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The first part of Table I shows the number of series of injections given to these cases. Almost 96 per cent received two series or less. The second part of Table I shows the number of months of treatment that each case required. With added experience fewer patients were treated longer than three months. The case requiring forty-two months (five series) was cured by removal of the cervical focus. Eighty-six per cent of these patients responded in two months or less.

Table II presents the cases of patients (13.3 per cent) under treatment for three months or longer. The patients who had colpotomies were treated after operation except for one who developed an abscess during the first series of injections.

Part one of Table III presents the complications found in those patients who required two or more series of vaccine. In part two, showing the number of cases requiring three or more series, attention is drawn to the outstanding number of patients with residual cervical infection.

TABLE II. PATIENTS REQUIRING TREATMENT FOR THREE MONTHS OR LONGER

Required treatment	9
Chronic cervicitis	5
Colpotomy done	5
Uterine retroversion	2
Pyosalpinx	3
Total	24

TABLE III. COMPLICATIONS FOUND IN PATIENTS REQUIRING TWO OR MORE SERIES OF VACCINE

REASONS FOR TWO OR MORE SERIES	CASES	REASONS FOR THREE OR MORE SERIES	CASES
Irregular treatment	3	Irregular treatment	
Chronic cervicitis	11	Chronic cervicitis	5
Colpotomy	5	Colpotomy	
Required treatment	18	Required treatment	1
Abdominal operation advised	3	Abdominal operation advised	
Pyelitis	1	Pyelitis	
Uterine retroversion	1	Uterine retroversion	1
Total	42	Total	7

TABLE IV. CASES REQUIRING OPERATION

Colpotomy	12
Bartholin abscess	3
Conization of cervix	12
Cautery of cervix	12
Abdominal section	7
Abdominal section refused	3
Total	49

Table IV presents those patients whose condition required both surgical and medical care (28.4 per cent). The complication most frequently encountered was a residual cervical infection, comprising 48.9 per cent of all surgical complications. Abdominal section was advised in 5.8 per cent. Interestingly, three of this group refused operation because they were relatively free of symptoms but still carried a mass that was diagnosed as pyosalpinx.

RÉSUMÉ

The intradermal administration of foreign protein in the treatment of pelvic inflammatory diseases is practical, more safe, and less uncomfortable for the patient.



All of the details of technique as specified in previous publications were rigidly adhered to in our series. Fresh solution was always employed, and when not used was kept in an ice box. Two minims were injected with an intradermal needle in the skin of the ventral surface of the forearm and the resulting wheal was observed for at least half an hour. A positive reaction was indicated by an area of erythema varying in diameter from 7 to 40 mm. around the site of the original injection; this signified an absence of pregnancy. A negative reaction was taken to signify pregnancy. In addition, 2 minims of normal saline solution was injected into the opposite forearm for control purposes.

This series is composed of 523 cases. Preparatory to this series 50 patients of known pregnancy were tested at random just to acquaint the authors with the possible variations of the reaction. It was during this period that the first discouraging factor was encountered, namely, the great number of atypical reactions. Ordinarily pregnant patients should show no erythema, but three definite types were found:

a. The immediate temporary reaction: In this group a few patients developed an immediate erythema which disappeared in five to ten minutes.

b. Delayed temporary reaction: In this group several patients developed an erythema after twenty minutes or more which lasted for about ten minutes.

c. Delayed prolonged reaction: In this group there were several patients in whom, after about six hours, an intense erythema developed which persisted for about twenty-four hours.

These reactions were not like those described as a positive reaction over 7 mm. which developed generally in a few minutes and persisted for a period of half an hour or more, indicating an absence of pregnancy.

The second discouraging factor was found when 100 nurses, through the cooperation of the Superintendent, were tested as controls. Of this group, 12 developed no reaction, signifying a positive test for pregnancy. There were, of course, no nurses pregnant in this group, and a 12 per cent error was obvious, therefore. Furthermore, 50 female patients of the medical convalescent ward, definitely not pregnant, were skin tested with the following results: 5 developed no reaction, signifying a positive test of pregnancy. Likewise, 50 patients from the male convalescent ward were skin tested with the result that 8 developed no reaction, signifying a positive test. The large discrepancy in this control series was very disappointing.

From the prenatal clinic 300 patients were picked at random for skin testing, irrespective of age or duration of pregnancy. Of this group of known pregnant patients, 21 developed a definite positive reaction signifying an absence of pregnancy. The discrepancy in this group was 7 per cent. Two patients in whom ectopic pregnancy was suspected were skin tested and showed a positive reaction which contradicted the diagnosis. Both of these patients were operated upon and, as the tests had indicated, there was no pregnancy.

Because so many patients in a municipal hospital are colored and this test would not be applicable, an effort was made to develop the conjunctival test. This was done by instilling two drops of antuitrin-S

The results obtained in the present series are briefly:

1. Eighty-six per cent required treatment, two months or less.
2. Ninety-six per cent required two series of six injections or less.
3. Twenty-eight and four-tenths per cent of these patients required some surgical procedure during the treatment of their illness. Only 5.8 per cent were advised to have radical abdominal surgery; only 4 per cent consented to abdominal section.

NOTE: I wish to express my appreciation for the untiring effort and cooperation of the resident and attending staff without which this work would not be possible.

REFERENCE

Yates, H. W., and Davidow, D.: J. Michigan M. Soc. 30: 931, 1931.

1551 WOODWARD AVENUE

ANTUITRIN-S SKIN TEST FOR EARLY PREGNANCY

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THE necessity for a rapid, inexpensive, and reliable test for pregnancy has stimulated for the past ten or more years a great deal of clinical and laboratory research. Unfortunately most of the optimistic claims for one method or another have been disproved by collaborative work on these tests. The various techniques have been numerous, each having a definite group of supporting investigators and varied periods of popularity. The Visscher-Bowman chemical test of the urine and the Gruskin-Schwartz antigen skin test are but two of these. Certain men have placed much confidence on the observation of the vascular tree.

More recently a considerable amount of work has been done, using antuitrin-S skin test as a means of rapid diagnosis of early pregnancy. Gilfillen and Gregg and others stimulated new interest in this test because of their very promising claims, in spite of the fact that others had tried the same test with very discouraging results. In its favor are the simplicity of its administration and the rapidity of diagnosis; on the surface the test seems well-founded physiologically.

The test is based upon the fact that associated with early pregnancy and continuing for many months, there is found a tremendous rise of the anterior pituitary-like hormone. It has been reported that the hormone excreted will rise from 150 units to over 100,000 units in the first month or two of pregnancy; there is a complete drop by five days post partum. It would seem natural, therefore, that in a pregnant patient saturated with this hormone, the introduction of a small quantity of this same substance intradermally should elicit no reaction. On the other hand, the same quantity introduced in a nonpregnant patient should stimulate a positive reaction.

SUMMARY AND CONCLUSIONS

1. So far as the authors can ascertain, this is to date the largest case series in which this test has been employed.
2. Rigid adherence to detail, critical analysis, and interpretation of results were attempted in the hope of ending the controversy upon this subject.
3. All questionable cases were carefully followed up or had a Friedman's test performed.
4. The conjunctival test was not adaptable as an adjunctive procedure.
5. The test requires a moderate amount of experience in order to acquaint the clinician with the typical and atypical reactions.
6. The reactions apparently do not vary with the age of the patient.
7. A positive test (negative reaction) only lends weight to a suspected diagnosis of pregnancy.
8. Its value is limited in colored patients.
9. This test is not an adequate substitute for the Friedman's or Aschheim-Zondek test.
10. Results: Of the pregnant patients, 93 per cent were diagnosed correctly and 7 per cent incorrectly. Of the nonpregnant patients, 72 per cent were diagnosed correctly and 28 per cent incorrectly.

Our appreciation is expressed to the Superintendent of Nurses, Gallinger Hospital, Washington, D. C., for the cooperation of the 100 nurses used in the control series; to Dr. Paul Dickens, George Washington University Medical School, Department of Medicine, for his generous supply of antuitrin-S; and to Dr. Howard F. Kane, Professor of Obstetrics and Gynecology, George Washington University Medical School, for his kind cooperation in the preparation of this paper.

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Mönckeberg in considering the etiology of vaginismus emphasizes that spasm which is palpably due to an organic lesion may often have had a psychic initiation. Each case must be investigated with patience and understanding. The author recommends the use of a cocaine ointment in selected cases in which it is felt that a demonstration that intercourse can actually be effected will give the needed reassurance to the patient.

Gradual dilatation with bougies should accompany psychotherapy when indicated. Having the patient bear down and contract the abdominal muscles strongly facilitates the introduction of the dilator as the vaginal sphincter and transverse perineal muscles relax at that moment. In some cases of dyspareunia, Mönckeberg makes a vertical incision through the posterior fourchette and underlying muscles, partly within the vagina and partly through the perineum. The incision is closed transversely, increasing the size of the introitus. Coitus is allowed after one month.

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into the conjunctiva at the same time the forearm test was performed. Unfortunately, after several hundred tests this procedure was abandoned because the eye shows an extremely poor response even when the forearm showed reactions as large as 20 mm.

TABLE I. PATIENTS AND CONTROLS SKIN TESTED WITH ANTUITRIN-S

DIAGNOSIS	NUMBER OF CASES	NEGATIVE REACTION	POSITIVE REACTION	PERCENTAGE OF ACCURACY
Definitely Pregnant	300	279	21	93
Nonpregnant				
a. Nurses	100	12	82	88
b. Convalescent female patients	50	5	45	90
c. Convalescent male patients	50	8	42	84
d. Post partum: 5 days—2 weeks	11	8	3	28
e. Abortions (complete)	10	6	4	40
f. Suspected ectopic pregnancy (ruled out by operation)	2	0	2	100

TABLE II. COMPARATIVE ANALYSIS OF RESULTS

AUTHORS	PREGNANT		NONPREGNANT	
	% CORRECT	% INCORRECT	% CORRECT	% INCORRECT
Porges-Pollatschek	71	29	95.4	4.6
Gilfillen-Gregg	100	--	100.0	--
Hoffman-Fough	71	29	80.0	20.0
Parsons	66	34		
Frank-Wahrsinger	68	32		
Mandy-Mandy	93	7	72.0	28.0

The average duration of pregnancy, which gave a positive pregnancy test, was four months; the shortest was in one patient who reported to be five days overdue in her period. Many positive tests of pregnancy were found in patients only one month pregnant by history. All questionable cases where any doubt existed were either checked by careful follow-up or by doing a Friedman's test.

In reviewing Table I, it is interesting to note that the incidence of correct results was much higher in the pregnant group than in the nonpregnant group. It is also interesting to note that so high a percentage of patients from five days to two weeks post partum persisted in showing positive tests for pregnancy even when laboratory data have shown that the hormone excreted practically disappears after five days post partum.

In reviewing Table II, it should be mentioned that Frank and Wahrsinger used a variety of preparations but did get a 68 per cent accuracy with the antuitrin-S. However, from the entire series, 98 per cent gave a positive (nonpregnant) skin reaction. Dr. Susanne Parsons, in her work, has felt that all hormonal preparations, regardless of the variety or by whom used, have proved universally unreliable.

evidence of fetal bones, due to movement of the baby. He showed radiographs of a monstrosity. The fetus could not be demonstrated in the first anteroposterior film but was present in the lateral and second anteroposterior views. He explained the lack of demonstration in the first study as due to a state of continuous motion of the fetal structure which did not allow a shadow to be cast.



Fig. 1.—First anteroposterior roentgenogram of the mother's abdomen, revealing a single pregnancy.

This is the only reference in any journal, as far as I could ascertain, of the complete obliteration, due to fetal movement, of all fetal structures in the radiograph. This report was published in *Radiography* by the Eastman Kodak Company. The author of the article is a technician and not a physician.

THE FETAL MOTION FACTOR IN THE ROENTGENOGRAPHIC DIAGNOSIS OF PREGNANCY*

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THE purpose of this paper is twofold: First, to demonstrate the possibility of error in roentgenographic diagnosis of pregnancy due to movement of the fetus, and second, to give a few suggestions in technique, possibly to eliminate this error.

The roentgen ray has proved very helpful to the medical profession in the diagnosis of pregnancy. There are, however, certain weaknesses in this valuable method of diagnosis. It was noticed recently in one of my patients that a twin pregnancy showed evidence of only one baby in the radiographic study. Further studies then brought out the shadow of the two babies.

A search was made through the literature. It became evident that the roentgenologists have been aware of the value of lack of fetal motion in the production of good pictures of the baby in utero. It also became evident that the clinicians have not realized the possibility of the complete lack of demonstration of fetal structures in the roentgenogram due to movement of the baby. Several cases have been reported in clinical magazines, where a fetus failed to be shown on the film. Other causes, however, than fetal motion were attributed as the etiology for the lack of roentgenographic demonstration.

Grier¹ advised that both lateral and anteroposterior views should be taken in the roentgen study for pregnancy. He was of the opinion that in early and in multiple pregnancy, the lateral view is more reliable than the anteroposterior view. He stated that in the later months of pregnancy, however, after the fetal head has dropped into the mother's pelvis, the fetal head is not well seen in the lateral view because of being obscured by the pelvic bones. The head then shows better in the anteroposterior view, and the trunk and extremities in the lateral view. He gave several reasons which he thought made the roentgenographic diagnosis of twin pregnancy difficult. He stated that the mother's abdomen is always larger and often the amount of amniotic fluid is considerable. He thought that, if the pregnancy is early, these factors might prevent the demonstration of fetal bones in the anteroposterior view but that they would be seen in the lateral view, due to the rays not having to go through so much tissue. He further stated that in late twin pregnancy with one fetus a head presentation and the other a breech, the two fetal heads would be at opposite ends of the abdominal cavity and a 14 by 17 plate might be too small to show both heads. Then often the other bones might be too faintly outlined to demonstrate two babies.

Anderson² reported two cases of twin pregnancy where anteroposterior roentgenographic exposures showed only one fetus in each film. One of his cases was a vertex-breech presentation. He thought it likely that the 14 by 17 film was not large enough to show the fetal pole in the uterine fundus. He stated that in a case like his second, in which both fetuses were cephalic, that one of the heads must be posterior to the other and therefore only one skull might show in the anteroposterior view.

In 1939, McGaha,³ Chief Technician, X-ray Department, Touro Infirmary, New Orleans, Louisiana, advised as to the possibility of the radiograph's not giving

*Presented at a meeting of the Northern Minnesota Medical Association, at St. Mary's Hospital, Duluth, Minn., July 20, 1940.

the other in the lower right quadrant. There was, however, only a difference of five heartbeats between the two areas, the counts being 140 and 145, respectively. An area that felt like a fetal back was present in each anterior and lateral portion of the mother's abdomen. Consequently the roentgenographic study was done as previously stated on April 15, 1940.

Anteroposterior and lateral roentgenograms of the mother's abdomen were taken. The anteroposterior view showed one fetus, with the head in the pelvis, in occiput right position. The appearance of the bones seemed to indicate an eight months' pregnancy. A lateral view was then taken. Two fetuses were distinctly present, both heads were down, one head was in the pelvis and the backs were slightly posterior. An anteroposterior film was immediately retaken. This time there were distinctly two fetuses. Both heads were down. The right head was in the pelvis. The backs were on the right and left sides of the mother's abdomen. Both babies had the appearance of about an eight months' pregnancy. When the roentgenographic study was completed, the mother stated that there had been considerable fetal movement during the taking of the first anteroposterior picture. The films were taken each immediately following the preceding one; the same technique was used each time; two anteroposterior and two lateral views were taken; both fetal heads presented in the pelvis and the mother herself stated that there had been much movement during the first study. It is, therefore, thought by me that the movements of one of the babies was the sole cause of lack of fetal demonstration in the first study. I feel further that such factors as hydramnios, the rays having to go through too much maternal tissue, the film being too small as might occur with a breech-head twin presentation, omitting the lateral views and so not having a complete study, played no part in my case.

The patient had a spontaneous delivery of two identical male twins on April 29, 1940. They were born after approximately six hours of labor. The first baby weighed 2,335 Gm., and the position was occiput right posterior to occiput right anterior. The second twin weighed 2,680 Gm., and the position was occiput left posterior to occiput left anterior. The mother had an uneventful puerperium and the babies progressed nicely.

As I stated earlier, there have been a few cases of false roentgenographic diagnoses of pregnancy previously reported in the literature. Two cases were given by a physician. The reasons he attributed for the lack of x-ray findings were other than fetal motion. The other case was reported by a technician, not a physician. He felt that continuous fetal motion was the cause of his not being able to demonstrate the baby on his first film.

This motion factor has actually been utilized in certain fields in roentgenology. According to Jacobs,⁴ Ottonello,⁵ in 1930, described a method of producing roentgenograms of the entire cervical spine in posterior projection on a single film. This method consisted of the roentgenogram taken with the jaw in constant vertical motion. Several complete motions of the jaw must be made, open and shut, during the exposure. By this method the mandible is "fanned" out and does not cast a shadow on the film. It is thereby possible to show the cervical vertebra from the second down on one film.

Elward and Belair⁶ advised taking at least three roentgenographs so as to obviate the possibility of nonvisualization of fetal parts from movement. They also advised that a cleansing enema be taken several hours before the examination. They suggest that sufficient time be taken so that the patient does not become unduly excited. They think it a good plan to run an exposure or two first. This will show the patient the length of time necessary for her to hold her breath.

Hubeny and Delano⁷ believed that the lateral roentgenogram has not received sufficient emphasis for its value in the diagnosis of pregnancy. They advise the abdominal binder for compression of the abdomen and immobilization of the fetus.

The editor of *Radiography* suggested that the x-ray technician should forego the actual exposure until the fetus had stopped moving. He stated that a cooperative patient could tell when this had taken place.

CASE REPORT

Mrs. E. L., a 22-year-old white primipara, was admitted to St. Luke's Hospital on April 15, 1940, for roentgenographic study of the abdomen. The first day of her last menstrual period was Aug. 10, 1939. Considerable movement had been felt since the latter part of December, 1939. The date of expectancy was May 17, 1940.



Fig. 2.—Second anteroposterior roentgenogram of the mother's abdomen, revealing a multiple pregnancy.

The prenatal period was uneventful, with the exception that as pregnancy progressed the patient's abdomen was larger than the usual size for a given gestational period. At the time of the eighth-month prenatal visit, April 15, 1940, it was thought that there might be two fetal hearts present, one in the lower left and

section was done; a living child was delivered which died shortly after birth. Patient's course was progressively downhill and death occurred six weeks after operation. Permission for autopsy was refused.

The following year, Baldwin³ recorded a case of primary carcinoma of the vagina in a 14-year-old white girl. She was two and one-half months pregnant when the diagnosis was made. In spite of inadequate radium therapy she continued on to term and was delivered by classical cesarean section; this case due to extensive pelvic infiltration was considered inoperable and was treated with x-ray alone. She became rapidly worse and died fifteen months after delivery.

Mengert,⁴ in 1935, reported a case of primary carcinoma of the vagina in a 21-year-old white primipara. This patient was admitted close to term with a history of a bloody, vaginal discharge which had occurred intermittently during the last trimester of pregnancy. On vaginal examination a slightly irregular, firm mass 2 to 3 cm. in diameter was palpated in the upper left fornix of the vagina. On direct vision the mucosa over the mass was slightly reddened, but otherwise normal. It was thought to be a cervical fibroid which would not complicate vaginal delivery, since it would rise with the formation of a lower uterine segment. After thirty-six hours of labor the cervix was only 10 cm. dilated and the tumor mass was larger than before. Delivery was effected by craniotomy and embryotomy. The patient was discharged on her nineteenth post-partum day, the nature of the mass still unknown, to return in two months for excision of the growth. She returned later with urinary retention and increasingly severe constipation and was, in general, very ill. Vaginal examination was difficult for the vagina barely admitted one finger; the entire vagina and pelvis were infiltrated. Biopsy revealed primary epidermoid carcinoma of the vagina. She died several days later from uremia. Autopsy revealed generalized involvement of the pelvis, vagina, and peritoneal cavity.

Russell,⁵ in a recent report, recorded a case which closely parallels our own. He reported a case of primary squamous cell carcinoma of the vulva in a 19-year-old negress who at the time of diagnosis was in the seventh month of pregnancy. After radical vulvectomy she was delivered at term by cesarean section. The patient was further treated by radium and deep x-ray therapy and at the present time (after five years) shows no evidence of local recurrence or distant metastasis.

Age Incidence.—According to previous writers, malignancy of the vulva and vagina rarely occurs before late middle or old age. Williams⁶ states that primary carcinoma of the vagina generally occurs between the ages of 50 and 60 years. In Rothschild's tabulation of 331 cases of vulval carcinoma, the incidence was greatest in the 60- to 70-year group. Hoffman,⁷ reporting a series of 20 cases, found only 3 below the age of 50, and all were in the fourth decade. Taussig, quoted by Ludwick,⁸ stated the average age for carcinoma of the vulva to be 59 years, and in another report the same author found that 60 per cent of the patients were over 60 and 30 per cent over 70 years of age. Baldwin, who has reported the youngest case accompanying a co-existing pregnancy, gives in the same communication the age distribution of 28 uncomplicated cases of vulval carcinoma. The greatest incidence occurred between 65 and 70. There were none under 30 years. In our case and in the five cases collected from the literature the ages vary from 14 to 33 years.

CASE REPORT

M. U., Case No. 117172, a 26-year-old, white female, gravida iii, para 0, was first seen in the Dermatologic Outpatient Dispensary on March 25, 1939. She complained of a large fungating mass of the right labia which had been present for the past seven months. It had started as a small, hard mass about the size of a marble and had steadily increased in size. Three months before admission it had ulcerated. At the same time she had noticed several pea-sized warty nodules on the left labia majora which had not grown during the last seven months. There was no history of syphilis or of inguinal lymphadenopathy. Her last menstrual period had been on Sept. 8, 1938. She had noticed marked breast changes and progressive increase in the size of her abdomen. She had not received any prenatal care nor had she consulted a doctor about the labial lesion until March 21, 1939, when she presented herself at the Health Center Prenatal Clinic for examination.

They instruct the patient to take a breath and hold it several seconds before making the exposure. They feel that this helps to quiet fetal movement.

DISCUSSION AND SUMMARY

From a search through the literature, it is evident that the roentgenologists have been and are aware of the value of lack of fetal motion in the production of good pictures of the baby in utero. It is, however, also evident that the clinicians do not realize the value of this moving fetus factor. As far as I could ascertain, no cases of complete obliteration of fetal structures have been reported by clinicians in the literature.

It is suggested that, in order to eliminate if possible this diagnostic error, the lower bowel and bladder should be empty at the time of examination, both anteroposterior and lateral roentgenograms should be taken, and the exposure not made until both the mother and fetus are quiet.

I am indebted to Dr. Gage Clement of the X-ray Department, St. Luke's Hospital, and Dr. Arden L. Abraham of the X-ray Department of St. Mary's Hospital, Duluth, Minn., for their help in the interpretation of the radiographs.

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PRIMARY EPIDERMOID CARCINOMA OF THE VULVA COMPLICATING PREGNANCY

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PRIMARY squamous cell carcinoma of the vagina and vulva is reputed to be a disease of the aged. When found complicating pregnancy in the young, it is indeed rare. Five cases of carcinoma of the external genitalia associated with pregnancy have been reported in the literature.

Review of the Literature.—The first case of squamous cell carcinoma of the vagina complicating pregnancy appeared in the French literature in 1929, reported by Audebert and Estienny.¹ This patient was a 33-year-old white multipara who had had slight genital bleeding and a serosanguineous discharge since the fifth month of pregnancy. She was in labor six hours, membranes had been ruptured artificially, but the head failed to engage. Consultation revealed a large tumor mass that had infiltrated the entire posterior vaginal wall. The child was delivered successfully by cesarean section. Biopsy was reported positive for squamous cell carcinoma of the vagina. The mother at the time this case was reported was alive and attending the cancer center for radium therapy. There was no complete follow-up in this case.

Tuft² in 1930 reported a case of carcinoma of the vagina associated with pregnancy in a 16-year-old negress. She was first seen when she was about seven and one-half months pregnant. Vaginal examination at that time revealed a cauliflower-like mass involving the upper two-thirds of the posterior vaginal wall, extending to the cul-de-sac but not involving the cervix or anterior vaginal wall. Biopsy showed squamous cell carcinoma of the vagina. The patient received preoperative radiation by means of radium needles implanted in the mass. Several days later cesarean

taken on March 25, 1939, and was reported as epidermoid carcinoma, Grade III malignancy. X-ray examination of the pelvis and long bones showed no evidence of metastasis. After consultation between the Obstetrical, Gynecological, and Tumor Service, the following plan of treatment was decided upon:

1. Simple vulvectomy immediately to remove the local tumor mass and not to disturb the co-existing pregnancy.

2. Cesarean section when pregnancy had progressed sufficiently to insure a living child.

3. Bilateral radical groin dissections (Basset operation) as soon after delivery as patient's condition would permit.

4. Deep and superficial x-ray therapy to groin and vulva as soon as surgical wounds were healed. Radiation would also affect castration.

March 31, 1939, following our plan, a simple vulvectomy was done under general anesthesia by Dr. J. Heiman of the Gynecological Service. The patient was discharged with good results on May 8, 1939, to Prenatal Clinic. (Fig. 2.) No evidence of local recurrence was found.

On June 13, 1939, the patient, then in her eighth month of pregnancy, was admitted to the hospital for cesarean section. A classical section was done so as to avoid dissemination of tumor cells. A 6-pound 3-ounce male infant was delivered in good condition. The postoperative course was afebrile and the mother and baby were discharged on June 26, 1939.

The patient was readmitted on Oct. 4, 1939, for radical groin dissection. The lapse of time between the cesarean section and the groin dissection was much longer than originally planned because the patient refused to come in for operation. However, on Oct. 6, 1939, under gas-ether anesthesia, the femoral and inguinal glands on the left side were radically excised. Because of the length of this procedure only one side was done at that time. The right groin was dissected on Oct. 16, 1939. The pathologic report on the tissue removed showed no evidence of malignancy and the diagnosis of chronic lymphadenitis was made.

The period of convalescence was complicated by the filling of the dead space in the right groin with a serosanguineous sterile fluid which required repeated aspiration. On Nov. 14, 1939, the patient was discharged and referred back to the Tumor Clinic.

X-ray therapy was begun on Nov. 30, 1939, and completed Dec. 14, 1939. A total of 1400 r. units was given through 15 by 15 cm. ports to each groin, and a total of 1200 r. units was given directly to the perineum through a 10 by 10 cm. port. The factors were 200 K.V.; 15 MA; T.S.D.—50 cm.; 1 mm. Thoreus filter.

The patient was again hospitalized on Dec. 18, 1939, for incision and drainage of a subcutaneous abscess which had developed in the region of the right groin dissection. She also had a low-grade thrombophlebitis and cellulitis of the right leg and foot. After drainage of the abscess and conservative therapy to the leg, she convalesced rapidly and was discharged on Jan. 19, 1940. At the present time (after seventeen months), the wound in the groin is completely healed and the patient is in excellent health. No evidence of local recurrence or distant metastasis of the carcinoma can be found.

SUMMARY

Six cases of primary epidermoid carcinoma of the external genitalia complicating pregnancy, including the present report, have been recorded in the literature. Four had their primary site of origin in the vagina. Three of these ended fatally in a remarkably short time, the fourth patient was alive six weeks post partum. The final course is not known since the follow-up is incomplete. Two cases were primary squamous cell carcinoma of the vulva and were treated in a similar, though quite independent, manner. Both patients at the present writing are alive and well, one after a period of five years, the other after seventeen months.

The treatment of all operable carcinomas of the vulva is vulvectomy with complete bilateral inguinal dissection. This procedure must be tempered to fit the individual case when accompanied by pregnancy. The results of surgery for this condition are highly favorable. Taussig⁹ reported 20.4 per cent and Stoeckel¹⁰ a 31.2 per cent five-year cure rate. However, it is important to remember that these cases were not complicated by co-existing pregnancy.

She was then referred to the Cincinnati General Hospital where she was seen by the Dermatological, Obstetrical, Gynecological and Tumor Clinic Departments. A provisional diagnosis of carcinoma of the vulva associated with six and one-half months' pregnancy was made, and the patient was sent into the hospital for treatment.

Past History.—The patient had had the usual childhood diseases, and had had typhoid fever at the age of 16. She was treated for pellagra two years prior to the present admission.

Catamenia began at the age of 14 years, occurring every twenty-eight days and lasting for four days. Patient had no previous gynecologic disorders or operations. She had had two previous pregnancies, both terminating in spontaneous abortions at the third month.

Physical Examination.—Temperature was 98.6° F.; pulse, 80; respiration 20; and blood pressure, 125/75. Patient was a well-developed, well-nourished, young white female, and did not appear acutely ill or in distress. Examination of the heart and chest was essentially negative. Abdomen was negative except for an intrauterine pregnancy, extending 2 to 3 fingers above the umbilicus. Vertex was presenting and not engaged, back on left, small parts on right, fetal heart 142 and regular.



Fig. 1.



Fig. 2.

Vaginal Examination.—On the right labium majus a large ulcerated fungating mass, measuring 6 cm. in diameter, was found (Fig. 1). The base of the tumor had infiltrated the labia, but the mass was movable and not fixed to the deeper structure. It partially obstructed the vaginal introitus, but did not involve the vaginal mucous membrane. Scattered over the upper part of the right labium majus and over the entire left labium majus there were numerous papillary and pedunculated nodules which were firm, nontender, and varied in size from 2 to 8 mm. They appeared like typical condylomata acuminata. Internal examination revealed a soft, nondilated cervix which pointed down and forward. The uterus was enlarged to about six and one-half months' gestation. Speculum examination revealed no infiltration or abnormalities of the vaginal mucous membrane or cervix.

Rectal examination was essentially negative. Small, soft inguinal glands were palpated bilaterally.

Blood Wassermann and vaginal smears were negative. Frei tests were read as strongly positive on the left arm and negative on the right arm. A biopsy was

nausea, but no vomiting occurred. She had been on duty for over fourteen months with an aged male patient with a draining empyema cavity from which pneumococci and tubercle bacilli were said to have been recovered elsewhere. Except for an appendectomy about twenty years ago she had been well all her life; had never been pregnant and menstrual history had been unremarkable until four months previously, when a mild menometrorrhagia appeared and has continued. Last menstrual period was fourteen days before present illness. Coitus for the past two years was denied. There had been no cough or other respiratory difficulty. Examination revealed: Temperature, 100.4° F.; pulse, 96; respirations, 20; nose and throat clear and without discharge; lungs without evidence of pathology; abdomen, an old right rectus incisional scar, tenderness 1-plus in both lower quadrants, no spasticity or rebound pain; pelvis, a profuse, greenish yellow, blood-streaked discharge from the cervix, pain 4-plus upon motion of the cervix, especially upon lifting it forward, pain 3-plus to 4-plus throughout the pelvis, with generalized thickening but no masses, palpation difficult and unsatisfactory due to extreme pain. Smear made from the cervical discharge (Gram stain) showed many pus cells, polymorphonuclears; many red blood cells; many gram-positive extra-

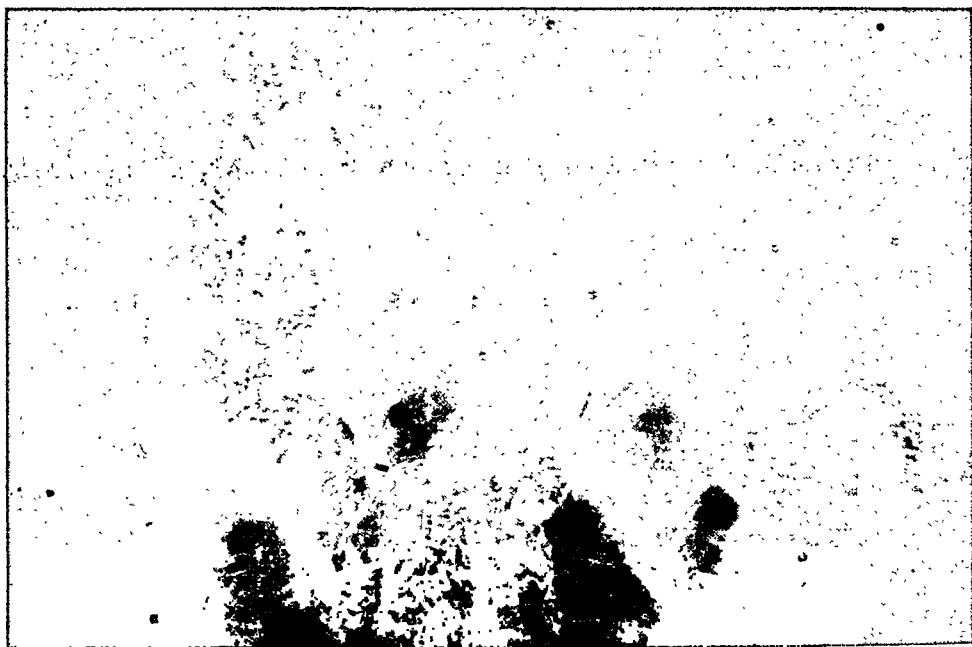


Fig. 1.—Photomicrograph of cervical smear, showing gram-positive extracellular encapsulated diplococci.

cellular encapsulated diplococci resembling pneumococci; no intracellular organisms. Material for typing and culture was obtained from the cervix upon sterile swabs and later taken to the hospital where it was reported they had dried to such extent that typing was impossible; culture was made, nevertheless, but showed no growth. Complete blood count showed hemoglobin 60 per cent; red blood cells 3,280,000; white blood cells 12,950; Schilling differential, neutrophils 79 per cent, segmented 49 per cent, band forms 29 per cent, juvenile forms 1 per cent, lymphocytes 21 per cent. Early primary pneumococcal pelvic peritonitis was diagnosed, and she was admitted to St. Francis Hospital, admission No. 19233, at 6 P.M., April 15, 1940, where chest films showed no pathology. Sulfapyridine therapy was begun at once: 2 Gm. at each of the first 2 doses, four hours apart; then 1 Gm. every four hours, awakened if necessary; soda bicarbonate 4 Gm. with each of the first 3 doses of "sulfapyridine," then 3 times a day; fluids only as desired for the first eighteen hours, then to be forced to 3000 c.c. per twenty-four hours. pH of the urine was done at each voiding and remained at 7.5 throughout, otherwise normal. Nausea

According to Cutler¹¹ the effect of radiation therapy alone is difficult to evaluate. Variations in the character of the disease and the small number of cases studied constitute the chief difficulties. The difficulties surrounding radiation treatment of carcinoma of the vulva are due chiefly to the fact that the normal tissues of this region are so delicate and so sensitive to irradiation that it is exceedingly difficult to effect the sterilization of the carcinoma without serious damage to the normal tissues.

In the treatment of carcinoma of the vagina complicating pregnancy, surgery is not practicable. The therapy, therefore, is irradiation alone. Early diagnosis followed by the same thorough irradiation as is given for cervical carcinoma is important. The prognosis at best is poor.

• CONCLUSION

1. A case of primary epidermoid carcinoma of the labia majora complicating a six and one-half months' pregnancy in a woman of 26 years is presented.

2. Treatment was instituted according to the following plan: Simple excision of the tumor mass, cesarean section, bilateral radical groin dissection, postoperative x-ray therapy.

3. Five other cases of carcinoma of the external genitalia complicating pregnancy in young women were collected from the literature. We agree with Russell that more cases must have occurred but were not reported.

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PRIMARY PNEUMOCOCCIC PELVIC PERITONITIS IN AN ADULT; PROMPT CURE BY SULFAPYRIDINE THERAPY

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PRIMARY peritonitis due to the pneumococcus in an adult is not frequent; when it is confined to the pelvis, it is rare indeed. In 1938 Nuckols and Hertig¹ were able to collect from the literature but 77 cases; only 23 of these were not associated with a recent obstetric episode. In 1940, Bennett and Mengert² added 2 cases. In 1939, Barnett, Hartmann, Perley and Ruhoff³ reported the use of "sulfapyridine" in the treatment of pneumococcic peritonitis in 5 children, all of whom recovered. In 1939, Ladd, Botsford and Curnen⁴ recommended the use of "sulfapyridine" in pneumococcic peritonitis in infants and children. A search of the literature has not revealed a report of the use of "sulfapyridine" in primary pneumococcic peritonitis, pelvic or general, in an adult.

CASE REPORT

On April 15, 1940, Mrs. E. N., a graduate nurse, aged 41 years, widow for two years, presented herself at the office. Four days previously she had first noted a profuse, irritating, greenish vaginal discharge which was accompanied by a mild diarrhea and occasional cramps in the lower abdomen. Two days later pain appeared in both lower quadrants of the abdomen, and diarrhea and cramps became worse. The same day for the first time, she had a temperature of 101° F. and

DISCUSSION

Although Nuckols and Hertig¹ assume quite a positive position against an ascending infection in pneumococcic peritonitis, Tompkins⁵ thinks it fair to assume that pneumococcic pelvic infection in women is ascending unless there is a clear history to the contrary; and King⁶ believes that, whatever the etiology, the symptoms are the same for all organisms. The case presented certainly seems to be one of ascending infection; and, though successful culture of the pneumococcus from the cervical discharge would have been of corroborative value, the typical smear, together with the course and complete absence of subsequent findings in the pelvis, leave no doubt as to the correctness of the diagnosis.

COMMENT

1. A case of very early primary pneumococcic pelvic peritonitis has been reported.
2. Prompt cure was obtained by sulfapyridine therapy.

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LEFT RENAL AGENESIS, TRUE UNICORNUATE UTERUS, AND TOTAL ABSENCE OF LEFT BROAD LIGAMENT, ROUND LIGAMENT, SALPINX, AND OVARY*

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LESS than thirty cases of true unicornuate uterus with unilateral renal agenesis can be found in the available literature. Delaginiere,¹ Pestalozza,² Urban,³ and Duncan⁴ reported one case each in which the Fallopian tube and ovary were likewise absent. The salpinx, ovary, and almost all of the broad ligament were missing in a case described by Guizetti and Pariset⁵ in 1911. McCrae,⁶ Tschisch-towitsch,⁷ and Guthrie and Wilson⁸ recorded a total of three instances in which the tube, ovary, and all of the broad ligament were absent. The only case presenting unicornuate uterus with complete unilateral absence of broad and round ligaments, tube, ovary, ureter, and kidney, which we have been able to find in the literature is that reported by Dannreuther⁹ in 1923. The case which we are now submitting is identical to his even to the side of the anomaly but differs in that the patient had a cystic right ovary and had borne two full-term living infants.

Mrs. Y. R., white, housewife, aged 27 years, gravida ii, para ii, native of Louisiana, born of French parents, was admitted to the Charity Hospital (U. H. No. T-38-76722) on Nov. 24, 1938, complaining of "pain in the lower abdomen." The onset of her complaint dated to September, 1937, shortly after the birth of her second full-term living infant. The pain manifested itself as a "dragging sensation" in the pelvis and was frequently associated with a "feeling of pressure on the rectum." It was exaggerated by exertion and was sometimes accompanied by lumbosacral backache. Infrequently, nausea and vomiting occurred. A slight leucorrhea, presenting itself after delivery of her first baby, became very profuse, thick, and somewhat malodorous after normal termination of her second pregnancy. Local

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was experienced the following day, April 16, and that evening she was given intravenously 500 c.c. of one-sixth molar sodium lactate solution and 500 c.c. of citrated blood. The next day, April 17, "sulfapyridine" concentration in the blood was 6.65 and that afternoon the dosage was reduced to 1.5 Gm. every eight hours for 3 doses, when it was discontinued. Total amount of "sulfapyridine" given: 16.5 Gm. in 13 doses, from April 15, 7 P.M. to April 18, 8 A.M. Only liquids, but including gelatin mixture, were allowed through April 19. Because of the secondary anemia, 1 c.c. of "reticulogen," was given each day of April 17, 18, 19. Temperature fell to normal on April 16 and, except for a slight rise on April 18, remained down; pulse and respiration came to normal on April 16 and remained so.

On April 18 complete blood count showed hemoglobin 78 per cent; red blood cells 4,020,000; white blood cells 5,000; Schilling differential, neutrophils 71 per cent, segmented 58 per cent, band forms 12 per cent, juvenile forms 1 per cent, eosinophiles 3 per cent, lymphocytes 26 per cent. Blood culture taken on April

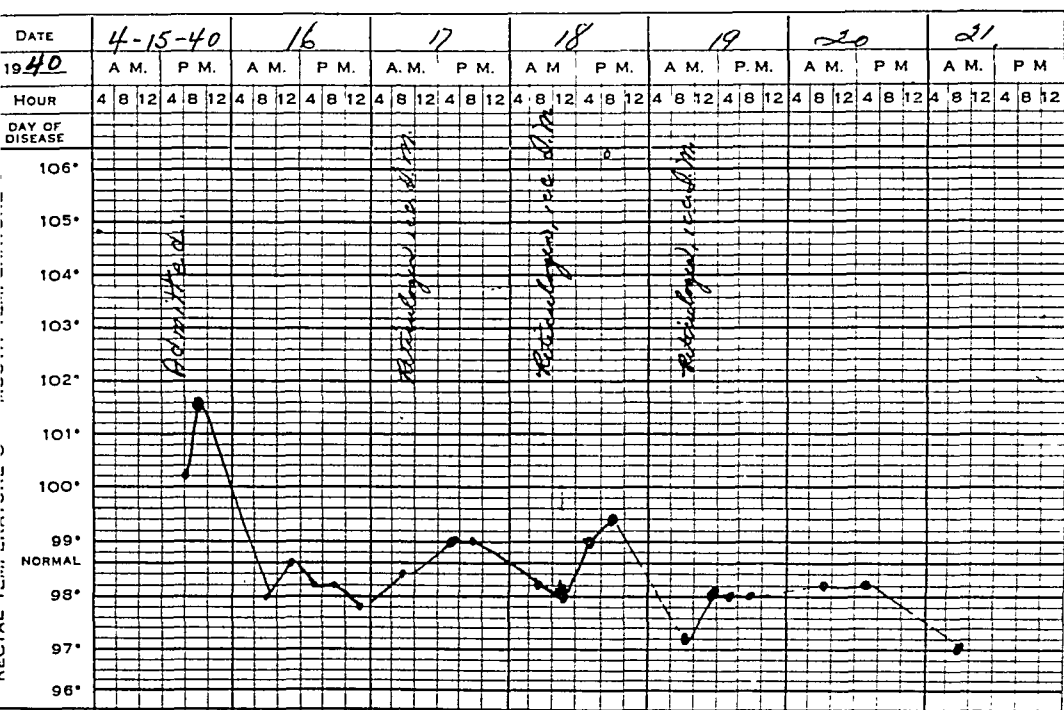


Fig. 2.—Temperature chart.

15, before sulfapyridine was started, showed no growth. On April 17 material for culture was again obtained from cervix and showed no growth; Gram stain of cervical smear showed many pus cells, few red blood cells and gram-positive bacilli, no intracellular organisms or cocci seen. Vaginal discharge and abdominal pain and tenderness ceased on April 18. She was discharged from the hospital on April 21 and remained free from symptoms, menstruating normally and painlessly from May 5 to 7, returning to the office for examination on May 9. There was no abdominal tenderness and no vaginal discharge; motion of cervix, including lifting forward, was painless; there was no thickening, mass formation or pain in either adnexal region or in the cul-de-sac; uterus was in fixed retroposition with a firm globular mass about 4 cm. in diameter in the fundus, probably a fibromyoma. Vaginal smear (Gram stain) showed occasional squamous cell, occasional red blood cell, few gram-positive bacilli, no intracellular organisms or cocci seen; hanging drop revealed no trichomonas.

findings, excluding those of the internal genitalia, were normal. Vaginal examination disclosed moderate relaxation of the perineum with a slight rectocele and a markedly lacerated, cystic, hypertrophied cervix. The uterus appeared to be of normal size, was retrocessed, second degree retroverted, and freely movable without pain. Traction on the cervix, however, did give rise to an expression of considerable discomfort. The right ovary was considerably enlarged and was in the culdesac. Neither tube nor the left ovary was palpable.

The studies of the blood and urine being normal, the patient was subjected to operation on Nov. 28, 1938, under ethylene anesthesia. After dilatation of the cervical canal, a Sturmdorf amputation of the cervix and Hegar perineorrhaphy were performed. The patient was then placed in a Trendelenburg position and the abdomen opened through a Pfannensteil incision. Palpation and inspection revealed the presence of a cystic prolapsed right ovary with complete absence of the left Fallopian tube, ovary, round and broad ligaments. The left iliac fossa



Fig. 2.—Hysterosalpingogram proves the right tube to be patent. There is dextroversion of the uterus. This roentgenogram was taken after 10 c.c. of 40 per cent skiodan solution had been injected into the uterine cavity.

was occupied by the sigmoid and rectum, and the vesical peritoneum followed the left margin of the uterus down to the vault of the vagina where it fused with the parietal peritoneum. The ovary being about 6 cm. in its greatest diameter, it was deemed advisable to resect the cystic portion. The uterosacral ligaments were then shortened after the technique of Kelly, and the right round ligament was plicated. Further support to the right ovary was obtained by shortening the infundibulopelvic ligament. The uterus was of the true unicornuate type, and its color and consistency were good. The right ureter was demonstrable, but the left was missing. No attempt was made to palpate the kidney areas due to the type of incision. The abdomen was closed in layers with absorbable material, and she made an uneventful recovery. An intravenous urogram was made to prove absence of left kidney. As shown by Fig. 1, the pelvis and calyces of the right kidney are well filled ten minutes after the intravenous injection of 20 c.c. of diodrast. No evidence of a kidney or ureter is seen on the left side in any of the three skiagrams obtained at 10-, 30-, and 60-minute intervals.

Although the patient attended the clinic subsequently, it was not until Jan. 24, 1940, that she consented to submit to cystoscopic examination and pyelography. On that date, a No. 24 Fr. Brown-Buerger cystoscope was introduced into the bladder with ease. Clear straw-colored urine was obtained. The bladder capacity was

cervical treatment in the Charity Hospital clinic proved effective only at times, and the cervical discharge was one of the major reasons that she applied for admission to the hospital.

Previous History.—Onset of menses at 14 years, with five-day periods of normal flow, occurring regularly every twenty-eight days. No menorrhagia, metrorrhagia, or dysmenorrhea prior to or since marriage. During her four years of marital life she has been delivered of two normal males. There had been no dyspareunia. She does not remember ever having any frequency of, or burning upon, micturition,



Fig. 1.—Right renal pelvis and calyces are well filled ten minutes after the intravenous injection of 20 c.c. of diodrast.

and the history is negative for hematuria, passage of stone, nocturia, pyuria, and incontinence of urine even upon coughing or sneezing. She stated that her urine had been examined several times without any abnormalities being found. Review of organic systems disclosed nothing of note, and her past history was irrelevant except for an uncomplicated appendectomy in 1921. Family history disclosed nothing of importance.

The patient was a well-nourished, apparently well-developed, highly cooperative, ambulatory, afebrile, intelligent person, whose blood pressure and other physical

within normal limits. There was no sign of a left ureteral orifice and no indication of an interureteric ridge. The vesical mucous membrane was normal, and there were no calculi, newgrowths, diverticula, or ulcers. The orifice of the right ureter was plainly visible. A No. 5 olivary radio-opaque catheter was introduced and passed into the right renal pelvis without any difficulty. Six cubic centimeters of clear urine were obtained. Five cubic centimeters of indigo carmine solution were administered intravenously and appeared in the urine in three and one-half minutes, being excellently concentrated in four and one-half minutes. Again inspection failed to reveal any indication of a left ureter. Twelve cubic centimeters of 40 per cent skiodan solution were injected and a pyelogram obtained. The right kidney showed evidence of compensatory hypertrophy and its pelvis and calyces were very slightly dilated. The renal pelvis was at the level of the lower border or the second lumbar vertebra. Both psoas shadows are visualized and there is no evidence of a kidney on the left. The patient was placed in an upright position and the ureteral catheter removed. The resulting pyelogram showed that the kidney descended to the lower border of the third lumbar vertebra, and the ureter could be traced. A week later, the patient returned for hysterosalpingography. Five cubic centimeters of 40 per cent skiodan solution were injected into the uterine cavity. The hystrogram was consistent with unicornuate uterus. Five additional cubic centimeters were injected and the hysterosalpingogram (Fig. 2) obtained. Dr. E. W. Brown, of the Charity Hospital X-ray Department, reported: "Views of the pelvis after injection of skiodan confirm the diagnosis of a unicornuate uterus. The latter is well visualized and the tube is patent." Study of the urine obtained at the time of cystoscopy was reported by Dr. Geo. Fasting as follows: "Bladder specimen: sediment negative, culture negative; right kidney specimen: many red blood cells and renal cells, culture negative."

Shumacker¹⁰ has so thoroughly presented the subject of congenital anomalies of the genitalia associated with unilateral renal agenesis that a review of the literature and discussion of embryology here would be superfluous.

SUMMARY

Less than 30 cases of true unicornuate uterus with unilateral renal agenesis have been reported.

Only one case of true unicornuate uterus with unilateral total absence of broad and round ligaments, salpinx, ovary, ureter, and kidney was recorded in the literature prior to this communication.

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Escomez, Edmundo: The Ovary of Lina Medina (The Youngest Mother in the World), Presse méd. 47: 1648, 1939.

The author describes the ovarian tissue containing the corpus luteum verum removed by the surgeon at the time of cesarean section upon Lina Medina, the five-year-old Peruvian mother. The ovary presented all the histologic characteristics of full maturity. Four fine photomicrographs are included in the article.

CLAIR E. FOLSOME.

TABLE I.—DATA ON CASES OF TRUE UNICORNUATE UTERUS WITH UNILATERAL RENAL AGENESIS (AFTER SHUMACKER¹⁰)

CASE	AUTHOR	UTERUS UNI- CORNIS	RENAL AGENESIS	URETER ABSENT	ADNEXA ON DEVELOPED SIDE	ADNEXA ON DEFECTIVE SIDE	AGE
1	Puech (1885)	R	L			Ovary in lumbar region; round ligament unconnected with uterus.	15 days
2	Roldtansky	L	R				76 yr.
3	Roldtansky	L	R				
4	Faltauf (1885)	L	R	R	Normal	Ovary long, in lumbar region; ovarian ligament extending toward inguinal ring; only ostial end of tube and round ligament present.	61 yr.
5	Winckel (1890)	R	L	L	Normal	Round ligament absent.	
6	Winckel (1890)	L	R	R	Normal	Ovary and tube solid and rudimentary; broad ligament absent.	
7	Brackenbury (1891)	R	L	L	Normal	Small rudimentary ovary above pelvic brim; no tube; broad and round ligaments rudimentary.	26 yr.
8	Naumann	R	L	L		Tube and ovary absent.	12 hr.
9	Delaginiere	L	R	R		Tube and ovary absent.	
10	Pestalozza	L	R	R		Tube and ovary absent.	
11	Urban (1899)	L	R	R		Ectopic ovary.	
12	Alglave (1905)	?	L	L		Tube, ovary and broad ligament absent.	40 yr.
13	McCrac (1908)	R	L	L		Tube, ovary and broad ligament absent.	
14	Tschischowitsch (1908)	R	L	L		Tube, ovary and broad ligament absent.	30 yr.
15	Guthrie and Wilson (1909)	R	L	L	Cystic ovary	Tube, ovary and broad ligament absent.	Fetus
16	Guizetti and Pariset (1911)	R	L	L	Normal	Tube, ovary and almost all broad ligament absent; round ligament attached to cervix.	11 mo.
17	Guizetti and Pariset	R	L	L	Normal	Ovary and ostial end of tube 1.5 cm. long; rudimentary broad ligament; round ligament attached to cervix.	14 yr.
18	Guizetti and Pariset	R	L	L	Ovary 9 cm. long	Ovary 6 cm. long; only ostial end of tube present.	13 yr.
19	Guizetti and Pariset	R	L	L	Normal	Ovary and ostial end of tube in inguinal hernia; only lower half of broad ligament present; round ligament attached to cervix.	
20	Guizetti and Pariset	R	L	L	Ovary 2 cm. long	Ovary 2.3 cm. long; only ostial end of tube present; only lower portion of broad ligament present; round ligament attached to cervix.	56 yr.
21	Boehme (1912)	R	L	L		Ovary in front of internal inguinal ring.	
22	Rosenthal (1913)	R	L	L		Ectopic ovary and tube.	
23	Oehler (1914)	R	L	L	Normal	Atrophic tube and ovary lying in hernial sac without connection to uterus; vessels from aorta and ventr. cava; broad and round ligaments absent.	59 yr.
24	Schilling (1917)	L	R	R	Ectopic ovary	Ovary long; incompletely descended; only ostial end of tube present; ovarian ligament and mesosalpinx fused with peritoneum of processus vaginalis; round ligament rudimentary.	1 day
25	Schilling	L	R	R	Normal	Ovary above linea innominata; only ostial end of tube present.	2½ days
26	Dannreuther (1923)	R	L	L	Normal	Ovary, tube, round and broad ligaments absent.	25 yr.
27	Duncan (1923)	R	L	L		Ovary and tube absent.	26 yr.
28	Shumacker (1928)	L	R	R		Ectopic ovary and tube; no broad ligament.	13 yr.
29	Varino and Beacham (1940)	R	L	L	Cystic ovary	Ovary, tube, broad and round ligaments absent.	27 yr.

broad fields of a compact layer showing distinct changes of a decidual reaction. Chorionic elements are not encountered, neither as chorionic villi nor as chorionic cells.

Diagnosis.—Decidua of early pregnancy (suggestive of ectopic pregnancy) (Figs. 1 and 2).



Fig. 1.—Endometrial biopsy showing decidua spongiosa.

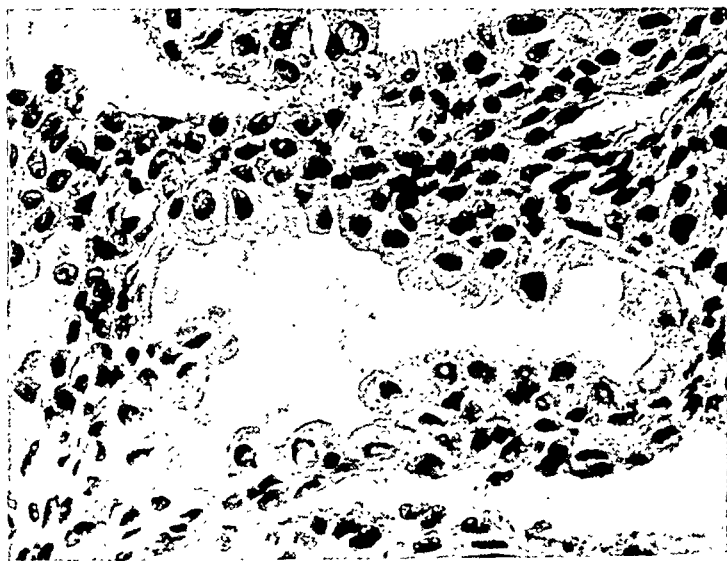


Fig. 2.—Detail of endometrial gland showing characteristic scalloped outline and dome-shaped cells.

The elapsed time between taking the endometrial biopsy and receiving the report of the frozen section was thirty minutes. Following this report, the patient was immediately hospitalized and prepared for operation.

At the time of operation, the uterus was found to be normal in size, but soft in consistency. A mass 10 cm. in length and 4 cm. in width was found, consisting of a distended right tube, which was firm and hemorrhagic. There was no free blood in the pelvic cavity. The left tube showed evidence of chronic inflammatory disease.

THE ENDOMETRIAL BIOPSY IN EARLY EXTRAUTERINE PREGNANCY

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THE endometrial suction biopsy is now an accepted diagnostic procedure. The histologic findings serve as an important guide to estimate the degree of both follicle and corpus luteum activity. Sturgis¹ has recently called attention to the importance of recognizing the characteristic glandular pattern seen in early pregnancy. In addition to the decidual changes of the stroma, stress is placed upon the appearance of the swollen epithelial cells which form the glands. They balloon out into the lumen with a free edge distinct and clear-cut, resembling exaggerated goblet cells. He concludes: "The characteristic glandular response described represents an increase in function consistent with early pregnancy."

The diagnosis of early extrauterine pregnancy still remains a difficult clinical problem. We rely upon a careful history, a painstaking physical examination, complete blood count, Aschheim-Zondek test, and in some instances, pelvic puncture. However, notwithstanding the attempts to establish a definite diagnosis, it is not uncommon to have a case of early ectopic pregnancy rupture while still under observation. Therefore, any further means of confirming this diagnosis may prove invaluable to the patient.

Suction endometrial biopsy was utilized in two cases of suspected extrauterine pregnancy. The histologic findings obtained were definite enough to warrant the diagnosis of early gestation. The cases are reported in detail as follows:

CASE 1.—A. J., aged 28 years, single, first seen Feb. 21, 1940, had been spotting for two weeks. Last period occurred Jan. 1, 1940. During the latter part of January the patient had low abdominal pain, intermittent in character, but not severe enough to cause confinement to bed. When she presented herself at the clinic as an ambulatory case, she did not look acutely ill. There was a blood-stained vaginal discharge. Bimanual examination disclosed a soft cervix, a small, rather firm uterus, and a mass, the size of a plum, in the right fornix. This mass was soft in consistency and moderately tender. Movement of the cervix caused no pain. A complete blood count showed: red blood cells, 4,250,000; white blood cells, 6,450; Hb, 80 per cent; polymorphonuclears, 65 per cent; lymphocytes, 32 per cent; eosinophiles, 2 per cent; monocytes, 1 per cent. Sedimentation rate was 20 mm. first hour. An endometrial biopsy was taken, from which a frozen section was made and examined by Dr. Grete Stohr, who submitted the following report:

The fragments are of appreciable size; the glands are densely distributed. Their trans-sections are wide and their lumina are serrated. The epithelial cells are broad, more square than columnar. Their apical portion is dome-shaped with clear protoplasm bulging into the lumen of the gland, or they are flat with frayed inner edges, with large, pale nuclei. In other, less frequent instances, they are corkscrew-shaped with folded columnar epithelium. The stroma is composed in

columnar type, alternating with stretches of lower cells, according to their location at the top or bottom of infolding crests. Nuclei are near the base of the cells; the entire cell substance is finely vacuolated, and the clear apical portion of the cells, when conformed to a row, produces a transparent scalloped border against the lumen of the gland.

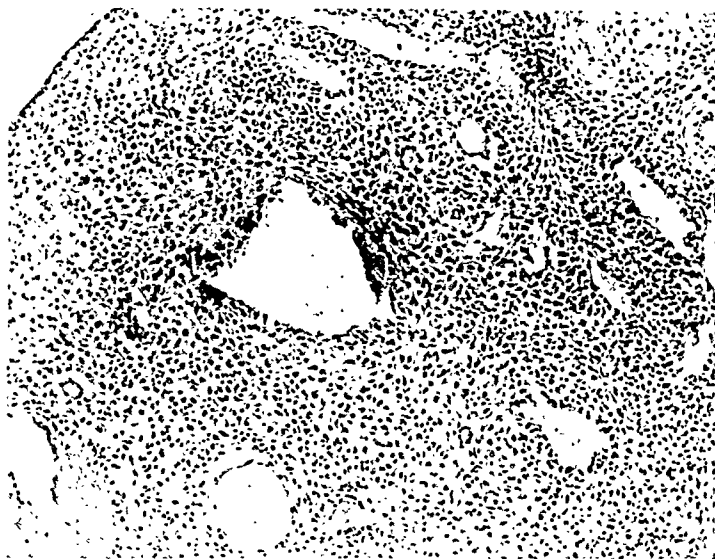


Fig. 4.—Endometrial biopsy; compact decidua; large stroma cells.

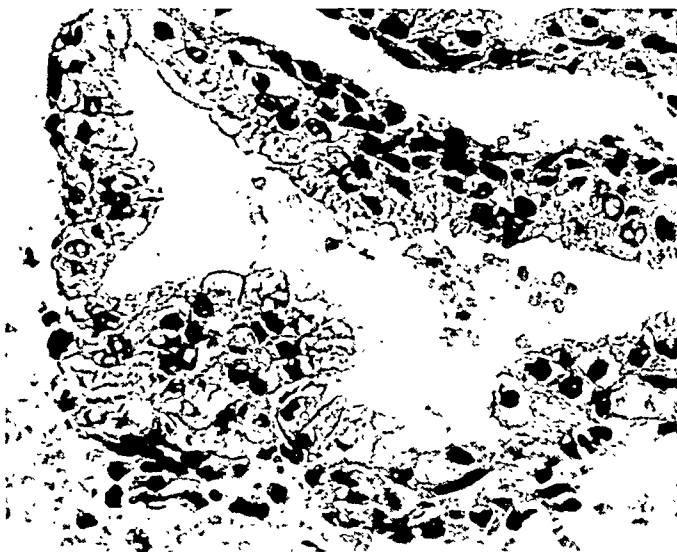


Fig. 5.—Characteristic gland with cells showing clear protoplasm and dome-shaped contours.

Diagnosis.—Decidua of pregnancy. Chorionic elements not found. (Indicative of ectopic pregnancy.) (Figs. 4 and 5.)

Laparotomy was performed immediately upon the report of the endometrial biopsy.

At operation, the uterus was small and appeared to be normal. The right adnexa were missing. On the left side there was a mass the size of a small orange. This mass consisted of an adherent left ovary, containing a large corpus luteum. Sur-

Pathologic Examination.—The right tube was transformed into an ovoid structure 9 cm. long and 5 cm. at its widest diameter. Cross section through the tube showed a partially formed placenta which penetrated through the entire thickness of the wall. The abdominal ostium of the tube presented a wide opening 2 cm. in diameter. The umbilical cord emerged from this opening; it was attached to an embryo 70 mm. in length, found just outside the ostium.

Microscopic section of the wall of the right tube showed partial or complete consumption of the tissues by implantation of the placenta, while other portions revealed a well-preserved tubal wall (Fig. 3).

Diagnosis.—Right tubal pregnancy and tubal abortion.

The patient made an uneventful recovery following her operation, and was discharged from the hospital in good condition.

CASE 2.—M. H., aged 32 years, married, was first seen March 24, 1940, complaining of lower abdominal pain. Last period occurred Feb. 22, 1940. On March 22, the patient had lower abdominal pain, which subsided on application of heat. The following day, the patient was seized with intense abdominal pain which caused a

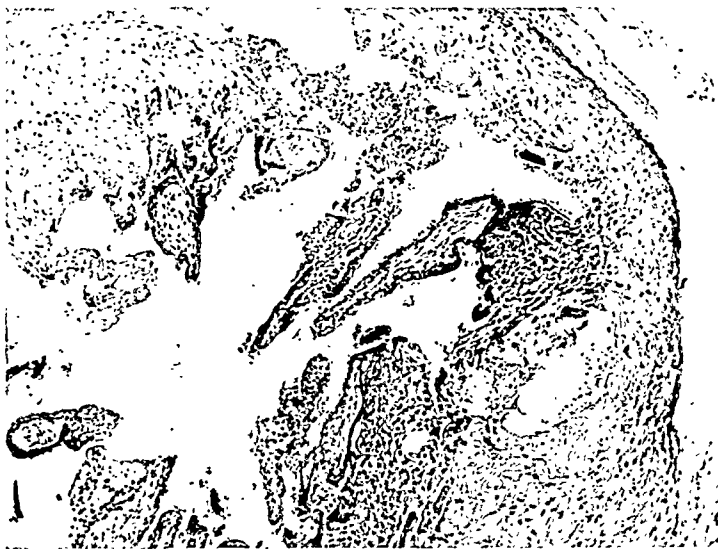


Fig. 3.—Section of tube showing implanted chorionic villi.

restless night. The pain was continuous, accompanied by slight vomiting. The pain became localized in the left lower quadrant. Concomitant with the onset of pain, there appeared a dark reddish-brown vaginal discharge which did not resemble a normal period.

Past History.—Operation in June, 1937, for endometriosis, with removal of right adnexa. She had been married for ten years, but had never been pregnant. Upon physical examination, the abdomen revealed no tenderness or rigidity. Upon vaginal examination, there was a brownish discharge. The cervix was not tender upon motion. The uterus was small, retroplaced. In the left fornix was a tender mass the size of a hen's egg, rather hard in its lower aspect, and softer in its upper portion.

Complete blood count: Red blood cells, 3,230,000; white blood cells, 6,650; polymorphonuclears, 68 per cent; lymphocytes, 32 per cent; Hb, 67 per cent. Sedimentation rate, 32 mm. first hour.

Endometrial suction biopsy was taken and the following report was submitted by Dr. Grete Stohr:

The fragments of endometrium were examined in frozen section. They are built of typical decidual stroma cells in which large tortuous, greatly serrated glands are embedded. On cross section, they have the characteristic rosette shape of the actively functioning gland. The epithelial cells are generally of a medium tall

with uterine decidua had a negative Friedman test. They state there is a close but not perfect relationship between the result of the Friedman test and the state of preservation of the chorionic villi.

Recently, TeLinde and Henriksen³ have reported a number of cases with decidua-like changes in the endometrium without pregnancy. Many of these occurred in endocrine disorders in which increased progesterone activity was present. However, they state that "curettage is often of great value in the diagnosis of tubal pregnancy, but the microscopic picture must be interpreted correctly if it is to be of value."

It must be borne in mind that the endometrial study should not be regarded as the sole method of establishing the diagnosis. We must take into consideration the history and the clinical data, together with the histologic findings. Furthermore, it must be emphasized that endometrial biopsy should not be attempted if intrauterine pregnancy is suspected. Sturgis¹ performed 7 endometrial biopsies in intrauterine pregnancies without interrupting gestation. In our series⁴ of 500 endometrial biopsies, we encountered one instance of intrauterine pregnancy in a patient with functional uterine bleeding. The pregnancy was not interrupted, and the patient was delivered of a normal full-term baby. However, unless the history and physical findings are definitely suggestive of ectopic pregnancy, we feel that endometrial biopsy is unwarranted.

CONCLUSIONS

1. The characteristic picture of the endometrial stroma and glands in pregnancy can be obtained by endometrial biopsy.
2. The use of suction biopsy has proved successful in confirming a diagnosis of unruptured ectopic pregnancy in two cases.

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31 LINCOLN PARK

Haworth, Norah A.: Malnutrition and Debility in Puerperal Psychoses, *Lancet* 2: 417, 1939.

An analysis of a series of 117 cases of mental illness arising in connection with childbirth and requiring hospitalization was made in an attempt to determine what additional precipitating factors might have been present. Seventy-two of the patients recovered; 60 had already had one or more normal confinements and 12 have had one or more confinements since discharge from the mental hospital without developing mental symptoms.

The majority of the patients were underweight and in poor physical health, and about one-fourth had been exposed to severe economic or emotional stress. The author believes that these two factors may be of great importance in precipitating the mental disturbance and that many cases could be prevented by attention to nutrition, general health, and environmental conditions early in pregnancy.

CARL P. HUBER.

mounting the ovary was a dilated tube about 8 cm. long and 5 cm. wide. The tube was filled with clotted blood. The clinical diagnosis was tubal abortion.

Pathologic Examination.—The tube, which was surrounded by large, loose and adherent blood coagula, was examined in many sections. In the majority the mucosa was partly reduced to a few atrophic folds; in other instances, folds were hypertrophic, congested, but without any evidence of inflammation; the muscle layers were thin and likewise hyperemic. In one of the sections, approximately half of the tube wall formed the site of implantation of compact masses of trophoblast cells and chorionic villi, which had penetrated and consumed this portion of the tubal wall except for the most peripheral thin layer of subserous connective tissue. Here, occasionally short fragments of the muscle tissue were preserved. A complete rupture of the wall was not apparent in successive sections. The chorionic tissue was well-preserved without any evidence of disintegration. Diagnosis: Early tubal pregnancy (not ruptured) (Fig. 6).



Fig. 6.—Cross section of tube from site of placental implantation.

DISCUSSION

Endometrial biopsy, in two cases of early tubal pregnancy, proved a valuable aid in establishing a diagnosis. It must be emphasized that the biopsy should be performed at the hospital under strict aseptic technique, and the patient prepared for immediate operation if rupture should occur while manipulating the uterus. In our two cases, there was no ill effect whatsoever, from the biopsy procedure. In early extrauterine pregnancy, the endometrium, stimulated by progesterone, presents the characteristic changes in both the stroma and glands. Later on, if death of the fetus occurs, the decidua may be cast off, with subsequent change of the endometrial picture. This factor should be kept in mind in the interpretation of the histologic pattern of the endometrium.

Goldblatt and Schwartz² correlated the Friedman test and the phase of the endometrium in ectopic pregnancy. They found that no patient with a negative Friedman test had a decidual reaction at the time of curettage; and conversely, no patient

Pathology.—The original biopsy was reported as: "Sarcoma, spindle cell, possibly a leiomyosarcoma. Numerous mitotic figures. Ulcerated surface. Nests of squamous epithelium below the surface, but no carcinoma found."

X-rays of the chest, spine, and skull were negative for evidence of metastases, and on Sept. 21, 1939, the patient was operated upon. The polypoid mass protruding through the cervix was removed and the cervix closed. At laparotomy a total hysterectomy and bilateral salpingo-oophorectomy were performed.

Pathology report on operative specimen: Gross: A uterus measuring 8 by 4 by 6 cm. with adnexa intact. There was no evidence of fibroids. On opening the uterus, multiple (about 12) polypoid structures were found arising in the fundus. The largest were about 4 cm. long and had a stalk 4 mm. in diameter. These had been hanging through the cervix, producing the lesion which was biopsied. The serosal surface of the uterus was intact. Microscopic: Advanced adenocarcinoma of the endometrium infiltrating almost through the uterine wall. The large polypoid masses arising in the fundus consisted of spindle cell sarcoma as reported in the previous biopsy. There was some proliferation of the adenocarcinoma into this (Fig. 1).



Fig. 1.—Microscopic section under low power, showing areas of mutual invasion of carcinoma and sarcoma.

The postoperative course was uneventful. The patient developed a mild urinary tract infection which was easily controlled with neoprontosil. She was allowed up on the thirteenth postoperative day. She has reported to the Clinic regularly by letter, and was last heard from in June of 1940 at which time she stated she felt well. She has not, however, returned for follow-up examination.

CASE 2.—The patient, O. Z., was a 58-year-old white nullipara who was four years postmenopausal. She was admitted to the University Hospital June 14, 1940 with a six-month history of daily vaginal spotting which had been gradually increasing. For the six months prior to the onset of bleeding, she had had a watery leucorrhea of moderate amount. Past history and family history were noncontributory.

Examination revealed a well-developed, somewhat obese white female. There was moderate emphysema of the chest; blood pressure was 160/96. The external genitalia showed menopausal atrophy. The cervix pointed posteriorly and was small and conical. The fundus of the uterus was anterior, slightly enlarged, freely movable. No adnexal pathology was palpated.

THE SIMULTANEOUS OCCURRENCE OF CARCINOMA AND SARCOMA IN THE SAME UTERUS

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SARCOMA of the uterus is not common, and the simultaneous occurrence of primary sarcoma and carcinoma of the uterus is even more rare. Twenty-eight cases were found in the literature, to which two case reports are here added.

A review of the literature on the coincidental existence of carcinoma and sarcoma in the same organ reveals considerable confusion in terminology. Oskar Frankl¹ emphasized the necessity for careful use of nomenclature and suggested "carcinoma sarcomatoides" for a carcinoma with the growth characteristics of a sarcoma; "carcinosarcoma" for intimate mixtures; and "sarcoma plus carcinoma" in those cases where separate tumors could clearly be demonstrated. The classification, however, has not been universally followed, and evaluation of the reported cases is difficult. Hoffman,² for example, has recently reported a clear-cut case of separate primary neoplasms, using the term "carcinosarcoma." In an effort to avoid this confusion an attempt has been made in this paper to include only those cases which apparently demonstrate distinct fundal primaries of differing type.

On this basis, 28 cases of separate carcinoma and sarcoma of the uterus were found in the world's literature. Major's report in 1918³ included 12 cases, 8 carcinoma plus sarcoma, and 4 adenocarcinoma and sarcoma. In an extensive review of the literature in 1932, Warren and Gates⁴ added 10 more cases of carcinoma plus sarcoma of the body of the uterus. Owen's⁵ series of double malignancies in 1921 included no uterine neoplasms, while the figures of Newell⁶ in 1929 are included in the Warren and Gates report. Since 1932 6 more cases have been reported,^{2, 7-11} and the records of two additional patients are presented here.

CASE REPORTS

CASE 1.—The patient, V. M., was a 66-year-old white woman, para ii, who had passed through the menopause at the age of 50. Since that time, she had had irregular intervals of minimal spotting, the episodes occurring every one to three months and lasting twenty-four hours. For one month prior to reporting to the University Hospital clinic, she had also had postdouché and postcoital spotting. Three episodes of profuse bleeding during the last of August, 1939, resulted in her admittance to a local hospital, where a positive biopsy was said to have been obtained and the patient was transferred to the University Hospital Sept. 14, 1939.

Examination revealed an obese white female with a blood pressure of 210/90. Pelvic examination: The vaginal outlet was parous and showed menopausal changes. The cervix was irregular, friable, and bled easily on manipulation. There was a redundant polypoid growth extending through the cervical os. This bled profusely and was easily biopsied, large pieces of tissue coming away with a sponge forceps. Rectovaginal examination showed the uterus in the midposition, slightly larger than normal, movable, with questionable thickening in the right adnexal region.

Blood Kahn was negative. Hemoglobin 75 per cent, with a normal white count. The patient had occasional mild glycosuria while in the Hospital. The glucose tolerance curve was classified as the glycosuria of obesity type by the Diet Therapy Department.

suggested that the explanation lay in the fact that the risk of getting cancer was not spread evenly over the entire population, but over a portion of it. Cancer morbidity and mortality rates based on this reduced population figure would give a frequency of coincidental malignancy in agreement with that found in fact.

Claessan and Mathias,¹⁵ reviewing the subject of the simultaneous occurrence of carcinoma and sarcoma in the same organ, could find a total of only 72 cases reported in the world's literature, the organ most frequently involved being the uterus.

Herxheimer¹⁶ and Ewing¹⁷ in discussing the pathology of carcinoma and sarcoma in the same uterus, arrive at similar theories as to possible etiology: (1) The tumors may develop simultaneously (possibly due to the same cause acting on different tissues). (2) Proliferation of the epithelium at the base of a pre-existing sarcoma, or at the point where a submucous or mural sarcoma meets the epithelial layer, may lead to development of a carcinoma. (3) The stroma of the carcinoma may undergo sarcomatous change (Herxheimer). (4) Carcinomatous changes may occur in glands of a sarcomatous polyp (Ewing). Doubtless the carcinoma sarcomatoides which Virchow described was, as he suggested, a true mixed tumor in which both epithelial and connective tissue elements were represented in the neoplastic growth. Saphir and Vass, in 1939,¹⁸ expressed doubts that any of the then reported cases represented distinct co-existent primary neoplasms.

In both the cases here reported, however, true independent primary growths were demonstrated. While a coincidental fibroid nodule was found in the uterine wall of one uterus (Case 2), in neither patient was there definite evidence of the sarcoma's having arisen on the basis of malignant fibroid degeneration. It is interesting that in both cases the preoperative diagnosis on the basis of pathologic material was sarcoma. The coincidental existence of the carcinoma was discovered in each case after laparotomy. In both cases there was a distinct geographic separation of the two tumors in the uterus.

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Blood Kahn was negative. Hemoglobin was 92 per cent with normal red and white counts. Urine was negative other than a rare white blood count in the microscopic sediment.

On June 18, 1940, the patient had a diagnostic dilatation and curettage and conization of the cervix. The pathology report on the curettage was: Spindle cell sarcoma of a type that could have arisen from a leiomyoma. Neoplasm cellular and rather anaplastic.

After x-rays of the chest, spine, and skull were found to be negative for any evidence of metastases, the patient was operated upon on June 21, 1940. The cervix was closed and a laparotomy performed, total hysterectomy and bilateral salpingo-oophorectomy being done. No local pelvic involvement was found, at the time of operation, and the serosal surface of the uterus was intact.

Pathologic Report.—Gross: Uterus with cervix, tubes and ovaries. "In the anterior wall of the uterus there is a large friable cellular spherical mass about 4.5 cm. in diameter which protrudes into the uterine cavity. The free portion appears necrotic. Some portions of the mass show pearly whorled appearance. There is also a 2 cm. fibroid in the anterior wall without gross evidence of degeneration."

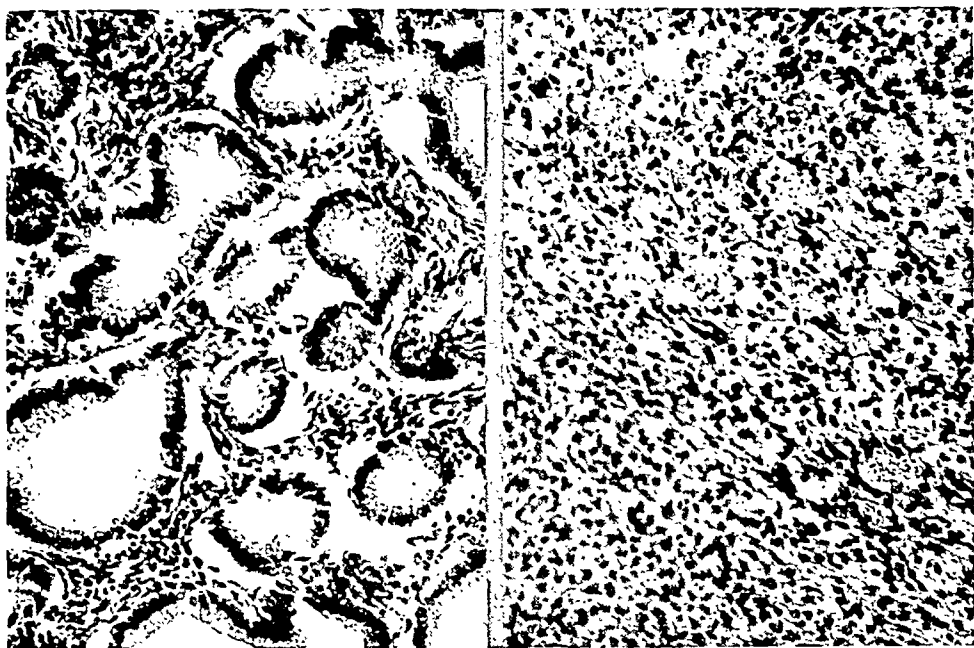


Fig. 2.—Area of adenocarcinoma (left) and sarcoma (right) from Case 2. No characteristic areas of overlapping of the two tumors were found.

Microscopic: Atrophy of the ovaries, parovarian adhesions and a small area of ovarian endometriosis. Uterus: Atrophy of the cervical glands with catarrhal cervicitis. "In addition to a large leiomyoma in the uterine wall, there is a confined malignant neoplasia of the endometrium, showing both spindle cell sarcoma as previously diagnosed and papilliferous adenocarcinoma. There is no evidence to suggest that one of these neoplastic types has been derived from the other. It seems rather that they have developed simultaneously." (Fig. 2.)

The patient's convalescence was uneventful, and she was discharged from the Hospital on her eighteenth postoperative day.

COMMENT

Statistical studies of reported cases by Warren and Gates,⁴ Burke,¹² Lund,¹³ and Burgher¹⁴ have all indicated that the incidence of double primary malignancies is higher than chance would indicate. Burgher

cysts with thick muscle walls may arise. The myometrium surrounding the island proliferates as it does around myomas. Robert Meyer² has described and collected 10 cases in fetuses and children (Fig. 1). In 7 of these cases, the island was found in the uterine fundus and in 3 cases in the cervix. Six of the 7 fundal islands were situated in the midline and all of the cervical islands were in the midline. Seven of the 10 islands were in the posterior wall and 3 in the anterior wall. These endometrial islands develop along with the normally situated endometrium. In some cases the aberrant endometrium undergoes the changes

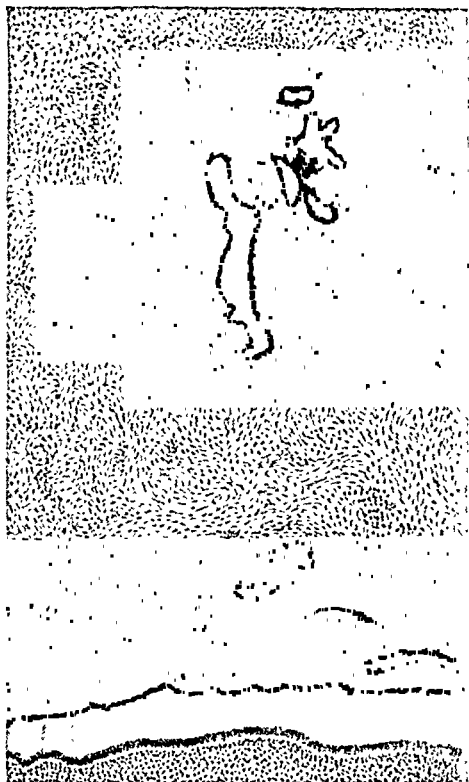


Fig. 1.



Fig. 2.

Fig. 1.—Transverse section through the uterine fundus of a newborn child. Note the uterine cavity below and the endometrial island in the midline of the dorsal wall.

Fig. 2.—Section through the nodule excised from a subserosal position on the left uterine wall. Note the small cavity in the shape of a cleft. The cavity is surrounded by a thick decidual layer. Surrounding this is a layer of longitudinal smooth muscle outside of which the muscle of the uterine wall is seen. Note also the scattered endometrial glands in the longitudinal muscle layer.

of the normal cycle, including menstrual necrosis. In other cases secretory changes and menstrual necrosis do not occur. One might postulate that the reason for this difference in behavior is dependent on the location of the island in the myometrium. If the aberrant endometrium is situated so as to be heavily compressed by the myometrium surrounding it, the endometrium may be prevented from reacting to hormonal influences. Decidual changes may occur during the time of pregnancy as demonstrated in our case. The island of aberrant endometrium may also act as a source for the development of an adenomyosis. The case to be described presents a minor degree of such adenomyosis (Figs. 2 and 3).

LOCALIZED ENDOMETRIAL REST IN UTERINE WALL

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ADENOMYOSIS of the uterus may be conveniently divided into three types on the basis of location. The first type is the well-known adenomyosis uteri interna which arises from the basal layer of the endometrium. Various local conditions in the myometrium, particularly pregnancy and sometimes inflammation, render the uterine muscle more susceptible to invasion by the endometrial tissue in a greater or less degree, producing the typical picture of uterine glands and stroma surrounded by myometrium. In this type, it is usually possible to demonstrate an original connection between the buried glands and the basalis of the endometrium. These glands respond to hormonal stimuli much as the basal glands of the endometrium. They do not ordinarily exhibit secretory changes during the luteal phase of the cycle but may show secretory change and rarely decidual reaction during the time of pregnancy. They do not undergo menstrual necrosis. About 50 per cent of the cases of adenomyosis uteri interna are combined with cystic glandular hyperplasia of the endometrium.

The second type is the so-called adenomyosis uteri externa. Here the endometrial glands are situated on or beneath the serosal surface of the uterus, and there is no demonstrable connection with the endometrium of the uterine cavity. These glands take their origin from several sources. Ectopic endometrium may be implanted on the uterine serosa from ruptured endometrial cysts of the ovary or endometriosis of the tube. Endometrial-like glands may arise, particularly in areas of adhesions between the uterus and surrounding structures, directly by a metaplasia of the serosal epithelium. This possibility is as yet a theoretical one and difficult to prove or disprove. There is also the remote possibility that the glands may reach the serosal surface by direct extension through the entire myometrium originating from an adenomyosis uteri interna as described above.

The purpose of this paper is to discuss briefly a third or intermediate form of adenomyosis which apparently has been overlooked by most writers and to present a description of a case in point. This third type arises from aberrant portions of Müllerian epithelium which have become separated from the Müllerian ducts during the stage of development of the genital tract, resulting in the production of separate endometrial islands in the myometrium. They represent, therefore, developmental anomalies. These endometrial islands may be found in any part of the uterus but are most often found near the serosal surface, producing at times visible projections above the surface of the uterus. Some cells of the Müllerian epithelium deviate in the earliest stage of development or, perhaps more often, during the confluence of both Müllerian ducts, thus forming separate endometrial islands (Fig. 1). From these islands large

Although the finding of aberrant endometrial islands has been described by Robert Meyer,^{1, 2} the English literature contains very little reference to such occurrences. Loyer³ reports the finding of an "interstitial endometrioma" in a 25-year-old female. A pea-sized nodule was found in the corpus uteri on the posterior wall. On cut section a central canal was seen, radiating out from which were numerous glands morphologically similar to endometrial glands. This probably represents a case similar to ours. Robert Meyer⁴ reports the finding of an endometrial rest in the midline of the posterior wall of the corpus of a six-year-old orangutan.

It is probable that a number of the cases reported in the literature as endometriomas represent aberrant islands of endometrium.

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MISSED ECTOPIC PREGNANCIES

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THE object of this paper is to stress the value of two simple procedures in preventing the tragic mistake of permitting the discharge from a hospital, of a patient who had a missed ectopic pregnancy, following a dilatation and curettage for what clinically appears to be an incomplete abortion. This error may be of greatest consequence in those hospitals in larger cities to which patients come from a distance.

Fortunately, some of these patients develop tubal rupture while still in the hospital. Such an experience four days after curettage on a patient, treated for supposed incomplete abortion, whose specimens had shown only decidual tissue, illustrates the necessity of never hurriedly discharging from the hospital a patient with these microscopic findings. If decidual tissue is found without chorionic villi, a negative Friedman test should be obtained before the patient is allowed to go home.

There seems to be some controversy in the literature regarding the association of decidual tissue with pregnancy.

Sampson¹ first pointed out that decidual change occurred in the endometrium associated with ectopic pregnancy. Willer² wrote that any polyp, removed as a cause of uterine bleeding, which showed decidual tissue indicated a pregnancy. A recent article by Te Linde and Henriksen³ stated that decidual tissue does not always mean a pregnancy. Therefore, the value of the Friedman test is particularly emphasized. Moreover Te Linde and Henriksen described a case in which an early embryo was found in the tube, but there was no decidual change in the stroma of the endometrium at dilatation and curettage. Siddall and Jarvis⁴ found that, when the curettage was done after ten days of bleeding, in ectopic pregnancy decidual tissue was not found in 100 per cent of the cases, and only 17.8 per cent showed decidual tissue when the bleeding persisted for more than twenty-nine days.

Case History.—A 29-year-old white female was admitted in the fourteenth week of her fifth pregnancy. She had a marked hypertension, and a diagnosis of chronic pyelonephritis and moderately advanced arteriolosclerosis was made. Her previous menstrual history was normal except for moderate lower abdominal cramps during the period of flow. Periods occurred every three weeks with a four- to five-day flow. It was decided that interruption of the pregnancy was indicated. An abdominal hysterotomy was carried out. At the time of operation, an elevated nodule about 3 cm. in diameter was noticed just beneath the serosa on the left uterine wall, immediately beneath the uterine end of the left tube. This felt hard on palpation, and it was thought to represent a subserous myoma. The mass was therefore excised. It was noticed, however, in the course of the dissection that the mass did not shell out as easily as might be expected.



Fig. 3.

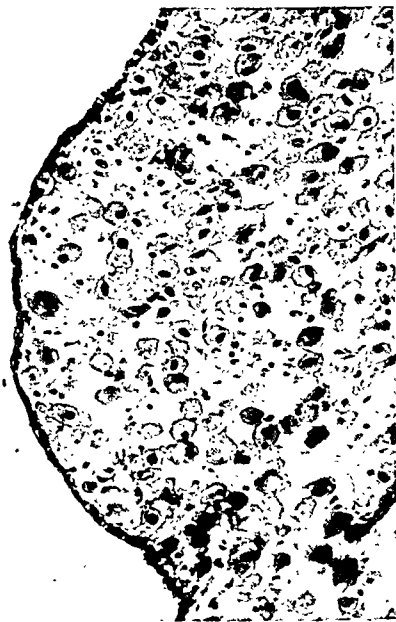


Fig. 4.

Fig. 3.—High power view of the secondary adenomyosis in the longitudinal muscle.
 Fig. 4.—High power view of the stroma lining the cavity. Note the large decidual cells.

Specimen.—*Gross:* The operative specimen measured 3 by 2½ by 2 cm. It was irregularly rounded. In its central portion a small lumen could be seen. This lumen was lined by a thick membrane. The wall adjacent to the lumen measured 1 cm. in thickness. There was no connection between the central canal and the surface of the uterus.

Microscopic Examination: (Fig. 2.) In a section through the nodule, a small cavity in the shape of a cleft was seen. The cavity was surrounded by a thick decidual layer. The inside surface epithelium was intact and composed of a single layer of cuboidal epithelium. Only a few small glands were seen in the basal area. The stroma had undergone a marked decidual change (Fig. 4). The stroma cells were large. They had a clear cytoplasm with small dark-staining nuclei which were situated eccentrically for the most part. The reticulum was very delicate. In some areas, a small amount of old blood pigment could be seen. Surrounding the endometrium was a layer of longitudinal smooth muscle outside of which the muscle of the uterine wall was compressed to form circular layers. Occasional scattered endometrial glands and stroma had invaded the longitudinal muscle layer (Fig. 3). The myometrium was edematous throughout.

Diagnosis.—Endometrial island in the uterine wall with secondary adenomyosis and decidual reaction.

Four days previous to this, she had severe cramp-like lower abdominal pain which lasted about one-half hour. On the following day this pain recurred twice. The Friedman test was again positive. At operation a small ectopic pregnancy was found in the right tube.

CASE 3.—R. F., 29-year-old white housewife, was admitted to the Roosevelt Hospital May 25, 1939, with the complaint of one month's amenorrhea, followed by four weeks' continual vaginal bleeding. Physical examination revealed the vagina bathed in blood, the uterus anterior, regular in outline, soft. The cervix was soft, boggy, and bleeding from the os. Adnexal regions were apparently normal. After forty-eight hours' observation, a dilatation and curettage were done. At this time a mass was felt in the left adnexal region, but it was decided to wait a few days and then run a Friedman test, before establishing a diagnosis of ectopic pregnancy. On the patient's third postoperative day she had exquisite pain in the left lower quadrant. On examination the abdomen was spastic, with maximum tenderness in the left lower quadrant. The left adnexal region was exquisitely tender and there was bulging in the cul-de-sac. Slides of the curettings showed only decidual tissue. The patient at operation was found to have a ruptured ectopic gestation of the left tube.

CASE 4.—J. B., aged 20, was admitted to the Roosevelt Hospital Aug. 4, 1935, complaining of vaginal bleeding of eight days' duration and lower abdominal pain of twelve hours' duration. Her course was similar to that of R. F., except that the tubal rupture occurred six days after the dilatation and curettage. Here again slides of decidual tissue only were available (which were of some value in a negative way of ruling out a postabortion parametritis).

CASE 5.—C. W., private patient, aged 32, was admitted to the North Country Community Hospital, Glen Cove, on Dec. 5, 1939, with the following history. A normal menstrual period was followed in five days by eight days of spotting about the size of a half dollar on a pad. A Friedman test was started the following day and was reported two days later as negative. The patient continued to spot for six days. At this time it was felt that the patient probably had an endometrial polyp and a dilatation and curettage were advised. Physical examination, when the patient was first seen after her eight days of spotting revealed a uterus about normal size, anterior, right ovary about the size of a small golf ball, and a small left adnexal enlargement, diagnosed as a hydrosalpinx about 2 to 3 cm. in diameter. Curettings revealed no definite polyp, but about the amount of tissue that would be obtained at this date in the patient's menstrual cycle.

In view of not finding gross pathology in the endometrial cavity, the Friedman test was repeated the day following the curettage. Two days later this was reported as positive. Inspection of the microscopic slides of the curettings showed secretory glands with a very slight decidual hypertrophy of the stroma. The patient was having no abdominal pain, and it was deemed advisable to repeat the Friedman test before deciding on operation. A repeat Friedman test was started the following morning. Thirty-six hours later the patient was taken with severe lower abdominal pain. Pelvic examination revealed a tender mass in the left adnexa. Abdominal operation revealed an ectopic pregnancy in the left tube and a cystic left ovary that was about 3 by 5 by 3 cm.

Two additional patients who were correctly operated upon for ectopic pregnancies after some time on the ward, had had criminal abortions attempted a week to ten days before admission. An admission diagnosis of a postabortion parametritis had been made.

DISCUSSION

Due to the low percentage of the "incomplete abortions" being really "ectopic pregnancies," one may rely too strongly on clinical judgment and discharge such patients. The grave consequences that may arise from allowing them to leave until the pathologic slides are checked, are apparent,

These facts led me to follow a further restricted policy of always obtaining a Friedman test before discharge on all unexplained bleeding in the childbearing years.

The case just referred to, as well as the experiences cited from the literature, prompted a study of the records of the Gynecological Department of Roosevelt Hospital for the past five years to determine whether this was a frequent accident. These records show:

Incomplete abortions	457
Incomplete abortions, later proved ectopic pregnancies ("missed ectopics")	4
Ectopic pregnancies	66

The four cases in which the error was made represent 0.9 per cent of patients with incomplete abortion treated during this period and 6 per cent of the cases of ectopic pregnancy.

In order to get a true value of material from curettage, 100 cases, diagnosed as incomplete abortion on discharge from the Roosevelt Hospital and proved so by clinical study at the recall clinic six weeks or two months later, were used as the basis for the study of their 100 respective endometrial slides. Of 100 clinically proved cases of incomplete abortion, the slides showed:

Slides with placental villi	75
Slides with considerable decidual tissue	21
Slides with early decidual tissue	1
Slides with slight decidual-like hypertrophy of endometrial stroma	2
Slides with only blood clot and too few cells for identification	1
	<hr/> 100

The following case histories include the four cases from the Roosevelt Hospital Gynecological Service and one private patient treated at the North Country Community Hospital, Glen Cove, Long Island:

CASE 1.—J. Z., a married woman of twenty-five years, was admitted on April 5, 1939, to the Roosevelt Hospital, complaining of amenorrhea and vaginal bleeding of four days' duration, her last period having occurred on the first of February. On March 27 she began to have slight spotting, and six days later there were sharp pains in both lower quadrants and continued slight spotting. Physical examination revealed a soft enlarged uterus. The cervix was slightly bluish and freely movable. The adnexa were negative. Friedman test was positive in two rabbits. Because of prolonged bleeding a dilatation and curettage were done on April 10. No adnexal mass was felt. Patient's postoperative course was normal. The patient was discharged. Pathologist's report of decidual tissue apparently was overlooked in view of the finding of a small mass of tissue during curettage, which was thought to be placental tissue. The patient was readmitted one week later with severe abdominal pain. A mass was noted in the cul-de-sac, and the Friedman test was returned strongly positive. She was operated upon and a ruptured right tubal pregnancy was found.

CASE 2.—A. R., married, aged 30, was admitted to the Roosevelt Hospital on Aug. 5, 1935, with a history almost identical with the above, except that an ectopic pregnancy was kept in mind, and the patient was allowed to go home for one week before repeating the Friedman test, as she lived adjacent to the Hospital. She was readmitted six days later, having bled steadily, saturating one or two pads daily.

time (and this was the last internal examination) revealed a closed cervix and an unengaged head. The pelvis was thought to be ample, but not roomy. It was decided that the patient was not in labor. She was given 3 gr. of nembutal and asked to remain in the hospital. The entire next day and night she had only slight abdominal pains. On the morning of March 18 the patient was still not in labor. The roentgenologic opinion was that the baby was normal in size, in R.O.P. position, the head was above the inlet, and that apparently there was no disproportion between the size of the pelvis and the size of the baby. Accordingly, it was decided that the patient was entitled to a real trial labor before any operative intervention was contemplated. She was discharged from the hospital and told to return at the onset of strong, regularly recurring, abdominal pains. She began to suffer such pains at about 9 P.M. that same day (March 18) and called at midnight to say that "her waters had broken." At 3 A.M., March 19 she entered the hospital, having rather strong uterine contractions recurring at five-minute intervals. Aside from the usual preparation and a hot soapsuds enema, she received no other medication.

At 7:30 A.M. she was having such strong contractions, lasting thirty to forty seconds, and recurring at two- to three-minute intervals, that she was decidedly uncomfortable, and 1/6 gr. of morphine sulfate was administered. This afforded her little relief. At 8 A.M. an abdominal examination revealed an unengaged head in R.O.P. position. It was decided that she had had an adequate trial labor, and therefore a low flap cesarean section was done at 8:30 A.M. March 19, under cyclopropane anesthesia. The blood loss was minimal, operating time 45 minutes. She was delivered of a normal male child, weighing 8 pounds 11 ounces, which cried spontaneously.

Her postoperative convalescence for the first five and one-half days was unusually smooth, the patient voiding spontaneously, complaining only of occasional gas pains, and having only three single elevations of temperature on three successive days, the highest of which was 100.6° F. and the lowest 100.2° F.

She was feeling especially well on March 24, beginning her fifth postoperative day, until 6:30 P.M. when she had a severe chill with a temperature of 103.6° F. Her only complaint was a short, dry, hacking cough. Examination at 8:30 P.M. revealed an acutely ill patient, having a temperature of 103.6° F., pulse 140, respiration 40. Breathing was labored, but not painful. The chest was free of signs except for a small area of dullness and diminished breath sounds at the right base. The abdomen was quite soft, not distended, and not tender to palpation. The wound was clean and dry, healing by primary intention, and showed no signs of tenderness or induration. Pelvic examination was deferred to the next morning when a cervical culture was to be taken. A catheterized specimen of urine at this time was negative except for a faint trace of albumin. A presumptive diagnosis of an embolic pneumonia arising from a pelvic thrombophlebitis was made.

It was because of this, i.e., that the pneumonia was thought not to be an inhalation pneumonia, and therefore probably not due to the pneumococcus, that the patient was placed on 20 gr. of sulfanilamide every four hours with 5 gr. of sodium bicarbonate, instead of sulfapyridine.

The next morning, March 25, the patient was worse, acutely toxic, markedly cyanotic, presumably as a result of the sulfanilamide, temperature ranging from 104.5° to 105.5° F. Aerobic and anaerobic plates were taken from the cervix, and aerobic and anaerobic blood plates were taken. A complete blood count, blood typing, throat culture (in view of the fact that no sputum was available), and portable x-ray of the chest were ordered. Pelvic examination at this time was noninformative. The uterus was involuting well, not tender. The parametria were clear, the lochia was normal in amount and color, and was not particularly foul. The x-ray of the chest showed a small, irregular patch of incomplete consolidation in the inner portion of the right lower lobe adjacent to the right border of the heart. The red cell count was 5,040,000 and 10½ Gm. Hb.; white count was 28,800, and 95 per cent polymorphonuclears.

Although she had received 160 gr. of sulfanilamide by the morning of March 26, the patient grew steadily worse. It was this morning that the blood culture taken the previous day showed a growth of approximately 1,200 colonies of *Staphylococcus*

It cannot be said from this study that placental tissue will be found in all cases of true incomplete abortion and decidual tissue in all cases of ectopic pregnancies, but it does suggest the following procedure:

1. Several slides should be made of the curettings, as one section may show decidual tissue, another placental tissue.

2. The microscopic slides of all patients before discharge from the hospital should be examined and, if placental tissue is found, the diagnosis may be considered correct, although uterine and extrauterine pregnancies do coexist in rare instances. If marked decidual tissue is obtained, the chances of the case being an incomplete abortion are good, but a Friedman test should be run before allowing the patient to leave. If only slight decidual-like change is noted in the stroma, the chances of an ectopic pregnancy existing are high and a negative Friedman test must be obtained before the patient is discharged.

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PUERPERAL SEPSIS DUE TO STAPHYLOCOCCUS AUREUS TREATED SUCCESSFULLY WITH SULFAMETHYL THIAZOL

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EVER since Domagk discovered that certain compounds containing the sulfanilamide radical have a pronounced chemotherapeutic action on beta hemolytic streptococci, research workers have labored in an endeavor to find new modifications of the parent substance which shall be either less toxic or possess a greater antibacterial activity on a wider range of organisms.

Barlow* and his associates have been successful in preparing two new sulfanilamide thiazol derivatives known as "sulfathiazol" and "sulfamethyl thiazol." Like sulfanilamide, they are effective against experimental streptococcal infections, and like sulfapyridine they have a pronounced antipneumococcal action, but unlike either of these preparations, they exert a pronounced effect upon staphylococci both in vitro and in vivo. Sulfamethyl thiazol, because of its increased toxicity and the occurrence of peripheral neuritis in 1 per cent of the cases, had been recommended only in severe staphylococcal infections endangering life, such as staphylococcal septicemia, pneumonia, and meningitis. Because of this, sulfamethyl thiazol has recently been withdrawn temporarily from investigational use and only sulfathiazol is available. It is hoped that in the near future a new substance will be presented to the medical profession, having as great antibacterial action but much less toxicity than sulfamethyl thiazol.

However, a case of severe staphylococcus septicemia successfully treated with sulfamethyl thiazol before its withdrawal is herewith presented.

L. T., a 35-year-old white primipara, had been married fifteen years. Her last regular period was June 12, 1939. Her pregnancy was uncomplicated except for a threat to miscarry during the first trimester. On the night of March 16 she entered the hospital complaining of regularly recurring abdominal pains. She was examined at 1 A.M. on March 17. The baby was in R.O.P. position, estimated at 8½ pounds, head unengaged. Although she was complaining of abdominal pains, there were no palpable uterine contractions. A rectal examination done at this

*Personal communication, Winthrop Chemical Corp.

for the first time. There was a peculiar discoloration of her skin resembling jaundice. There was an ecchymotic area about 3 inches long and 1 inch wide over the external malleolus of her right ankle which was tender to touch. Her temperature was 101.8° F. Her chest was negative on examination, although she still had a cough. Pelvic examination again revealed a perfectly normal, non-tender, firm, mobile, involuting uterus with no parametrial involvement. Sulfamethyl thiazol therapy was ordered cut, as it was thought that the patient was suffering from drug intoxication. Up to this time she had received a dosage of 10 $\frac{2}{3}$ Gm. of sulfanilamide and 78 Gm. of sulfamethyl thiazol, making a total of 88 $\frac{2}{3}$ Gm. or 1,330 gr. An x-ray of the chest the next morning showed no further extension of the pneumonic process. Her temperature had risen to 103.4° F., and there was insufficient involvement in either the chest or the pelvis to account for this. Her blood culture was sterile. A catheterized urine specimen was negative for pus, bile, or urobilinogen. The direct van den Bergh's test on her blood was negative. The discoloration of her skin was then thought to be due to the azo dye of the drug. Her blood count showed a definite leucopenia, having a total white count of 6,800 with 78 per cent polymorphonuclears. Forty-eight hours previous to this her count had been 18,400 with 77 per cent polymorphonuclears. There was no depression of her red cells or hemoglobin. She was given a transfusion of 500 c.c. of citrated blood. The next day, April 9, the white count was 6,000 with 61 per cent polymorphonuclears. However, despite this further depression of white cells, the patient was remarkably improved. Her temperature had dropped to normal. Her drowsiness had completely disappeared. The color of her skin was normal, and the ecchymotic area on the right ankle had faded. In her own words, "she felt like a new woman and had not a complaint in the world." With her temperature absolutely normal on the tenth and eleventh of April and with no complaints, a false sense of security was felt, so that no blood counts were done on those days. On April 12 the possibility of allowing the patient to dangle her legs was being considered when that afternoon she developed a temperature of 103.4° F. She appeared quite toxic. Complete physical examination was negative. That morning the wound had been dressed, found to be dry, with no discharge. The rubber dam which had been reinserted daily was now removed and left out. The wound was reinspected in the afternoon, probed, but absolutely no discharge was forthcoming. Complete blood count showed 3.39 million red blood cells with 10.5 Gm. Hb.; a white cell count of 1,750 with 4 per cent polymorphonuclears, and 9 per cent mononuclear cells. Her throat was absolutely negative. There was no evidence of angina now nor at any subsequent time. She was given 300 c.c. of citrated blood the next morning with 3 c.c. of liver concentrate (45 units U.S.P.) intramuscularly. Prior to this, a count done revealed 2,350 white blood cells with no polymorphonuclears. The only granular cells present were 2 per cent basophiles. She had 16 per cent mononuclear cells. The reason the percentage of mononuclears is mentioned is because some authors feel that the occurrence of a monocytosis in a granulocytopenia is a good prognostic sign. She was acutely ill for the two succeeding days, her temperature ranging from 101° to 104° F. She was given a transfusion on both of those days, receiving 500 c.c. citrated blood on the fourteenth and 300 c.c. on the fifteenth, and 3 c.c. of liver concentrate parenterally. By the morning of April 16 the patient was quite well again, her temperature being practically normal all day. Her blood count, which had been mounting steadily, had now reached 7,100 with 49 per cent polymorphonuclears. The majority of the polymorphonuclears were juvenile forms and their cytoplasm contained large, deep-staining, coarse granules which had been termed "toxic granules" but are only indicative of immaturity. The monocytosis continued increasing, reaching 19 per cent on the sixteenth of April. Strangely enough, with the blood count approaching normal, the wound began to drain pus again. Unfortunately, her blood count did not remain normal, but continued to rise so that she developed a leucocytosis. Her white count reached 19,350 with 74 per cent polymorphonuclears on April 20, and 20,700 with 85 per cent polymorphonuclears on April 29. As her white count rose, the percentage of young polymorphonuclears dropped to normal levels, and the so-called "toxic granules" disappeared. The percentage of mononuclears coincidentally dropped to normal levels. The patient felt quite well but continued to run

aureus per cubic centimeter. The uterine culture also showed a preponderance of *Staphylococcus aureus*, about 75 per cent, along with *B. coli*. Both anaerobic plates also showed *Staphylococcus aureus*, but no anaerobic organisms. The throat culture showed the usual bacteriologic flora, having some pneumococci and short chain streptococcic. The sulfanilamide was then discontinued, and sulfamethyl thiazol therapy was started.

At 1:45 P.M. of March 26, 2 Gm. of sulfamethyl thiazol were given by mouth and 1 Gm. every four hours from then on was ordered. Five grains of sodium bicarbonate were given with each dose of sulfamethyl thiazol. For the first few days, the patient complained of epigastric pain soon after taking the medication, which was quite severe, occasionally requiring codeine phosphate by hypodermic injection for relief. The pain, however, was of short duration and after a while it never recurred. There was no nausea nor vomiting, and the cyanosis was definitely less than that from sulfanilamide.

On the next day, March 27, although the temperature levels were a little lower, the patient complained of a painful right shoulder joint which was exquisitely tender on palpation, although not red nor swollen. It was felt that she was developing a septic arthritis, and this was more or less substantiated by the fact that coincident with the development of the painful shoulder joint there appeared about six small furuncles on the skin of her back and right buttock. Unfortunately, no cultures were taken from these although one on the buttock had to be incised.

Another blood culture and complete blood count were done on this day. The blood count showed a red cell count of 4,480,000 and 9.9 Gm. Hb.; white blood count, 23,400 and 95 per cent polymorphonuclears. She was given 250 c.c. of citrated blood. The blood culture the next day was reported as showing a growth of 240 colonies of *Staphylococcus aureus* per c.c. of blood. The dose of sulfamethyl thiazol was increased to 1½ Gm. every four hours. She was definitely improved on March 28. She was more comfortable, her temperature levels were lower, and she only had occasional spells of drenching perspiration which previously had recurred with annoying frequency.

Another blood culture and complete blood count were done on March 29. The blood count showed 3,660,000 red blood cells and 8.5 Hb.; white blood count 21,250 and 89 per cent polymorphonuclears. There was no growth in the blood culture in twenty-four hours, but in forty-eight hours there was a growth of 2 colonies per c.c. of blood. She was given a transfusion of 250 c.c. citrated blood on March 30.

A catheterized specimen of urine on March 30 was negative. Her improvement was marked by April 1. An x-ray of the chest taken then showed evidence of possible beginning resolution from a larger pulmonic field in the right lung than had been originally involved. The left lung was negative. A blood culture taken this morning (April 1) proved to be sterile. Her blood count was 3,260,000 red blood cells and 9.7 Gm. Hb.; white blood cells 18,800, and 85 per cent polymorphonuclears. The dosage of sulfamethyl thiazol was decreased to 1 Gm. every four hours. On April 2 and 3, the highest temperature level was 100.8° F. On the morning of the fourth the dosage of sulfamethyl thiazol was decreased to 1 Gm. every day. She had received 66 Gm. or 990 gr. up to this day. On the night of the fourth her cough was becoming more pronounced and her evening temperature rose to 102° F. This repeated itself on the fifth, so the dosage of sulfamethyl thiazol was increased to 1 Gm. every six hours. A blood count was done on April 6 and showed 3,400,000 red blood cells and 9.5 Gm. Hb.; 18,400 white blood cells and 77 per cent polymorphonuclears. The patient was feeling quite well, appetite excellent. Her only complaint was an annoying cough which was controlled with codeine, and an evening elevation of temperature to 102° F.

On April 1, on inspection of her wound, there was a small, superficial separation near the inferior angle from which a scant serosanguineous discharge could be expressed. On April 6 this discharge had become more profuse and definitely purulent. The opening was widened with a hemostat and a rubber dam drain inserted. A culture from the wound showed *Staphylococcus aureus*. However, there was no tenderness nor induration, and it was felt that the wound could not account for her fever. On the afternoon of April 7 the patient complained of drowsiness

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MATERNAL DEATH CAUSED BY HEMORRHAGE IN THE ADRENALS*

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SUPRARENAL hemorrhage in the adult is an unusual condition almost invariably associated with other pathology in the body. Extensive hemorrhage with parenchymal destruction and suprarenal failure has been found co-existing with and furnishing the immediate cause of death in a number of widely diverse conditions. Among these reported in the literature are cases of epilepsy, extensive neoplasm of right lung compressing the vena cava, metastatic carcinoma of the adrenals and other intraabdominal organs, agranulocytic angina, bacterial endocarditis, staphylococcus pyemia, meningococcal bacteriemia, and one of advanced diffuse arteriosclerosis with subacute nephritis. In the following case report, suprarenal hemorrhage and necrosis were co-existent with unilateral hydronephrosis and bilateral pyelonephritis. There has been no previous report, I believe, of this condition as a causative factor in maternal death.

Mrs. M. P. (Hospital No. 28556), a 35-year-old white multipara, was admitted to the Fitkin Memorial Hospital on June 23, 1939. She was the wife of a poor tenant farmer living in an isolated portion of Monmouth County; this woman had received and apparently needed no medical attention during the pregnancy which had advanced to the thirty-sixth week at the time of her acute illness and premature labor. Three children had previously been born to her at home, apparently without complications. The ages of the children are 14, 9, and 4. The physician who attended the confinement in all three cases knows of no disability or illness suffered by this patient. She worked hard continually.

The severely painful seizure which initiated the present illness began at 5 A.M. on June 23. The doctor who was called reached the patient's home at 7 A.M. and found her in extreme pain. The entire upper abdomen was rigid with great tenderness and pain in the right costovertebral region. There was no vomiting. The woman's pregnant condition was obvious, but it was questionable whether she was in labor or not. Hospitalization was advised because of the woman's acute illness and poor general condition. Blood pressure was not taken at home but the attending doctor thought the degree of shock was considerable. No morphine or other opiate was given.

Transportation to the hospital by ambulance was not effected until 12 noon. A marked state of shock was apparent at time of admission. The woman was conscious and cooperative. The pulse was rapid and almost imperceptible in the radial vessels. The respirations were labored. Blood pressure was 50/??, and

*Read at a meeting of the New York Obstetrical Society, May 14, 1940.

a low-grade temperature on certain days. The temperature and leucocytosis were cause for concern so far as there was nothing in the physical examination to account for them. The wound was practically healed and had only a scant purulent drainage. When her temperature reached 101.8° F. on May 1, the apprehension felt was sufficient to repeat a blood culture which proved to be sterile. It was only after the report of this culture was back that it was decided that her fever and leucocytosis were merely manifestations of bone marrow hyperactivity. So, throwing caution to the winds, she was allowed out of bed. Her temperature then found normal levels and remained so to the day of her discharge. Her white count, however, was 17,300 with 75 per cent polymorphonuclears on May 6, the day before her discharge. After fifty-three days in the hospital she was discharged on May 7 with her baby, who now weighed 10 pounds 3 ounces.

COMMENT

Sulfanilamide in the past has been most disappointing in the treatment of staphylococcus infections. The remarkable and dramatic response of this patient's sepsis to sulfanilamide's derivative, sulfamethyl thiazol, leaves little room for the argument of coincidence.

Agranulocytosis is probably the most serious complication that might follow the administration of sulfanilamide or its derivatives, so far as the large percentage of the cases (53 per cent in a study of the 30 cases reported¹⁻²⁶) developing this type of blood dyscrasia eventuate in death. The incidence of agranulocytosis with this form of chemotherapy is not particularly great and fortunately occurs only after prolonged administration of the drug. The smallest dose thus far reported as having given rise to agranulocytosis in an adult is 18 Gm.²⁴ and that patient recovered rather promptly. The average dose responsible for agranulocytosis in an adult was 57.7 Gm.¹⁻²⁶ Despite the infrequency of agranulocytosis as a complication, the gravity of its occurrence makes close vigil a sine qua non of prolonged administration of the drug. The late appearance of malaise, drowsiness, and unexplained fever calls for immediate withdrawal of the drug, even though the blood count may give no indication of an impending granulocytopenia. The precipitate suddenness with which granulocytopenia may occur is manifest in the case reported above.

The impression obtained from a study of 30 cases¹⁻²⁶ (including the author's case) of agranulocytosis following sulfanilamide therapy is that the prognosis depends not upon the treatment given but upon the severity of bone marrow depression that has occurred and the time of the withdrawal of the drug, i.e., a case has a much more serious prognosis if the drug has been administered up to the occurrence of agranulocytosis than if the agranulocytosis has occurred several days after the withdrawal of the drug.^{1, 14, 17, 24}

It is interesting to note that 16 per cent of those cases^{1, 14, 17, 24} had a monocytosis during the granulocytopenia and all of them recovered.

A study of the hematologic charts in the 30 cases referred to above showed that four (besides the author's) had a leucocytosis following the agranulocytosis but none of the authors commented upon the unusual nature of this occurrence, nor did they state whether there was anything present to explain the increased white count. However, in a very commendable article on agranulocytosis, Damashek reported the occurrence of a leucocytosis after granulocytopenia had first been artificially induced with amidopyrine and then withdrawn. He refers to it as a "release phenomenon." If a toxic depression of bone marrow can give rise to an acute illness with high temperatures, it does not seem unreasonable to assume that a hyperactive bone marrow in its regenerative phase can also produce some temperature and leucocytosis.

I should like to express my thanks to Winthrop Chemical Corporation for their kind cooperation, and to Mr. Joseph M. Chernaik for his invaluable assistance in doing the laboratory work.

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Urinalysis (catheterized specimen) June 24, showed specific gravity, 1.013; albumin, heavy cloud; and hyaline and granular casts; red blood cells and clumps of leucocytes were found in the sediment.

Blood count June 24, red blood count, 3,840,000; hemoglobin, 73 per cent; white blood count, 22,100, and polymorphonuclears, 87.

The autopsy showed 80 to 100 c.c. of fluid in each pleural cavity, with pneumonia of right lower lobe, congestion of left lung base, and pericardial effusion. Within the abdomen a fairly large amount of blood-tinged fluid was found, along with petechial hemorrhages into the mesentery and edema of the parenchymatous organs. On section the liver showed cloudy swelling and diffuse hemorrhage. Both kidneys were enlarged, the right more than the left. There was hydronephrosis on the right side and the kidney pelvis contained gravel and two stones. As the ureter entered the bladder three stones were impacted. Microscopic study of both kidneys showed pyelonephritis.

The adrenal glands were slightly swollen. Both showed pericapsular hemorrhages and on section there was also subcapsular hemorrhage infiltrating through the cortex into the medulla. Microscopic study showed normal structure nearly obliterated. In the best preserved portions the reticular and vesicular layers can still be made out in places but even here extensive hemorrhage is present. Low and high magnifications of the other places in the adrenal show extensive necrosis and hemorrhage without any characteristic adrenal cells. There was no blood vessel thrombosis.

CONCLUSION

Based upon clinical course and post-mortem examination findings it seems indisputable that the adrenal hemorrhage and necrosis was the cause of death in this case. (Toxemia dependent upon pyelonephritis seems the most reasonable predisposing factor in causation of this rare adrenal damage.) The nature of the acute seizure forty-two hours before death may be debated. Although the right ureter was obstructed by calculi impacted near the bladder orifice it seems unlikely that renal colic produced the initial pain. I believe that labor and delivery made little or no contribution to the state of shock, and pregnancy had nothing to do with any of the outcome. Adrenal damage is the probable explanation for the initial pain, abdominal rigidity, pyrexia, and shock. Adrenal insufficiency persisted and led to the fatal outcome, the terminal pneumonia being incidental.

DISCUSSION

DR. HERBERT F. TRAUT.—These microscopic preparations remind me very much of the pictures that have been published by Georgy and his co-workers of experimental animals which were given a diet deficient in choline. These animals showed not only the fatty type of degeneration of the liver, but also massive hemorrhage of the adrenals, involving, first, the medulla, and much later, the cortex of the adrenal.

I suggest this as the possible etiology. It is possible that the patient's diet was not adequate and that avitaminosis may have figured in the etiology of this case.

DR. SAMUEL H. GEIST.—As Dr. MacKenzie has stated the clinical diagnosis of adrenal insufficiency is extremely difficult. If, however, we are fortunate enough to make such a diagnosis or even suspect it, it might be worth while to try the effect of desoxycorticosteron, which might temporarily tide the woman over her primary shock and enable her to offer some resistance to an infection which might follow labor. What this therapy might offer I do not know but it is worth trying. Short of this we are absolutely helpless in the face of such a critical condition.

DR. N. M. ALTER.—While it may not be germane to the topic under consideration, I would, first, like to call attention to an article by Dr. Robert Frank in which he speaks of the adrenal being the master gland, probably taking the place of the pituitary gland, and that it has not been given the attention it deserves.

This case demonstrates that the probable indirect cause of death was the septicemia, but the direct cause was shock brought about by massive hemorrhage

rectal temperature 102.4° F. Severe abdominal pain was the chief complaint, the abdominal muscles were rigid, and uterine contractions were not definitely felt at first. After $\frac{1}{4}$ gr. of morphine and an intravenous infusion of 500 c.c. of 10 per cent dextrose had been given, the blood pressure was 70/30. Pulse was 132. Intermittent uterine contractions could then be felt. No fetal heart sounds were heard at any time. At 1:30 P.M. vaginal examination showed the cervix to be completely effaced and three fingers dilated. The membranes were ruptured artificially and amniotic fluid heavily stained with meconium escaped. Breech presentation was diagnosed. Within two hours spontaneous expulsion of a stillborn male fetus, weighing 2,870 gm., was accomplished, followed quickly by complete placental separation without unusual bleeding. One ampoule of ergotrate was given intravenously.

Subsequent to delivery the patient fell asleep and profuse diaphoresis was noted. The pulse became stronger, rate 120. Blood pressure was 80/40. The temperature at 4 P.M. was 98.8° F. and at 8 P.M. 98.2° F. Throughout the evening and night the condition remained much the same. The patient slept intermittently, was thirsty

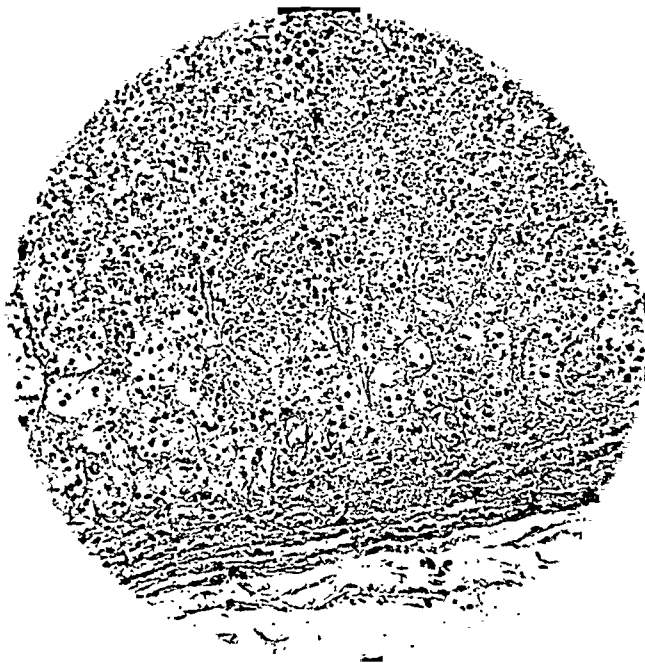


Fig. 1.—Section of adrenal showing hemorrhage. $\times 350$ diameters.

when awake, and took fluids well. Micturition was spontaneous. Blood pressure remained low, systolic 60 to 70. Color was poor. Intravenous infusions of 10 per cent dextrose were given in the evening and in the early morning, the latter after threatened collapse was evidenced by cold clammy skin, weakening pulse, and blood pressure of 40/?. At breakfast time the patient had rallied somewhat and enjoyed cereal. She also ate what was offered for luncheon and remarked that she felt fairly well.

Throughout the day, however, the extremities were cold and cyanotic, the pulse rapid and almost imperceptible, and the systolic blood pressure was persistently under 70. The abdomen was soft and not distended, the uterus firmly contracted, and lochia moderate.

About 6 P.M. sharp pain in right chest was mentioned and at 6:30 P.M. a "shaking" chill occurred. The breathing which had been labored all day became more difficult. Coarse moist râles were heard in both lung bases. In the evening cyanosis deepened and circulatory failure increased. Use of oxygen tent gave no relief. The patient died at 11:00 P.M. (thirty-two hours after delivery).

Vaginal examination showed marked thickening and cauliflower-like configuration around the urinary meatus. A granulation-like area at the side of the urethra presented a red papule that had been bleeding. The uterus was continuous with a firm mass which filled the left side of the pelvis and extended about 6 cm. above the pubic bone. A second vaginal examination, four days later, showed a hard nodule halfway up the posterior vaginal wall, about 3 mm. in diameter. It was not believed that this nodule had been present at the time of the first examination.

On Oct. 24, 1939, a Friedman pregnancy test gave a strongly positive reaction. The same day, a biopsy specimen was removed from the mass at the urethral meatus. The microscopic report showed "an invading chorioepithelioma. The tumor is composed of sheetlike masses of mononucleated tumor cells interspersed with many large multinucleated giant tumor cells. There is no stroma except around small blood vessels. The tumor is rapidly growing, is destructive in its invasive course in the normal tissue included in the sections. There is erosion and invasion of blood vessels and small hemorrhages; and there are numerous varying-sized areas of necrosis of tumor cells."

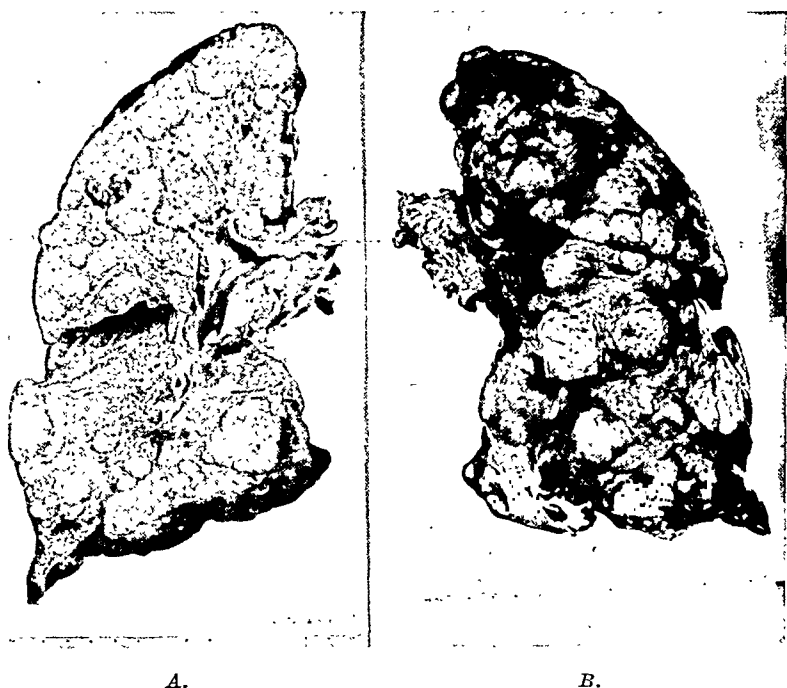


Fig. 1.—Metastatic tumor. A, Sagittal section of right lung. B, Posterior surface of right lung.

At the same time, an x-ray plate of the chest showed: "The lung fields present innumerable dense round areas of infiltration of different sizes. . . . The findings are those of malignant metastases. From the history and clinical findings, chorioepithelioma is the most likely origin of these metastases."

This patient, while in the Pratt Hospital, showed a remittent fever throughout three weeks. The temperature never went over 100° (F.). A total of twelve x-ray treatments were given to the front and back of the chest. In spite of these, both clinically and by x-ray examination of the chest, the tumor grew rapidly. The patient returned home. Later, there was urinary obstruction, uremia developed, and death occurred Feb. 2, 1940.

At autopsy, permission was not given to open the head.

Many findings were simply terminal in origin, and need not be listed here. The interesting ones, apart from the old pelvic adhesions, were a chorioepithelioma of the uterus, with metastases in the vagina, lungs, right kidney, and small intestines. The uterus measured 15 by 9 cm. The upper half, to the left, consisted of a round

into the adrenal. This has been known in obstetric practice, especially in infants and particularly in connection with marasmus, where we find it more extensive than it was in this particular case. In adults, the most common variety was that described in this country by George Cahill, in the adenomatous type of tumors, either malignant or benign. I had a case at the Margaret Hague Maternity Hospital where the woman died suddenly of unexplainable shock after parturition, due to an adenoma with no massive hemorrhage. In the case reported by Dr. MacKenzie the massive hemorrhage occurred in a practically normal adrenal without tumor formation, which, from a survey of the literature, is rather unique. I studied the sections submitted to me and the different portions showed barely recognizable adrenal structure; most of it was completely destroyed by hemorrhage and necrosis. The necrosis was due to vascular change, so there must have been some circulatory damage, but one cannot say whether it was due to septicemia.

I think that in this unusual case we should focus attention on the adrenal with the occurrence of sudden shock in a very acute, almost surgical, condition. In this patient the adrenal was practically normal before the lesion presented developed.

CHORIOEPITHELIOMA

ASSOCIATED WITH TUBAL PREGNANCY AND PULMONARY METASTASES.
HIGH GONADOTROPIN AND LOW PREGNANEDIOL VALUES.

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CHORIOEPITHELIOMA has been studied so extensively and so many cases of the condition have been reported, that only some features of special interest connected with the one we are presenting induce us to offer this summary.

This 37-year-old housewife was admitted to the Joseph H. Pratt Diagnostic Hospital, Oct. 18, 1939. She complained merely of "Not feeling good." For three or four weeks, she had been regurgitating a spoonful or so of whitish, sour, yellowish fluid upon arising in the mornings. There was a history of old gonorrheal infection. The family doctor had the patient admitted for study to decide whether the symptoms were due to pelvic inflammatory disease or to possible cholecystitis.

In January, 1939, she had had a ruptured tubal pregnancy (left). At operation, the tube and ovary were removed from that side, with excision of the uterine cornu. The right tube was tied. The patient made a fairly good recovery, complicated only by an attack of left-sided pleurisy. There was one almost normal period in March, 1939. There were none after that up to the date of admission to the Pratt Hospital.

She had been married eleven years, and had had two children, aged 10 and 7½ years. There was one induced abortion at two months about six years before admission. The only other pregnancy was the tubal one in January, 1939. On admission her weight was 135 pounds, a drop of 15 pounds from normal in a period of about six weeks. The blood pressure was 110/70. The urine showed a slight trace of albumin; no casts. There was mild secondary anemia; red blood cells, 3,510,000; and hemoglobin, 62 per cent. The blood sedimentation rate was always at a high figure, from 80 mm. to 90 mm. in one hour. The leucocytes were 7,300.

On careful physical examination, astonishingly few abnormal findings were discovered. The lungs seemed clear and resonant throughout; no râles were heard. The breath sounds were of good character; there was no adventitious rub at any point. This fact was demonstrated with special care on the left side, where there had been a pleurisy in January, 1939.

In the pelvic region, a rather hard nodular mass was felt just to the left of the midline above the pubis.

TABLE I

	PATIENT	NONPREGNANT, NORMAL	PREGNANT, NORMAL
Chorionic gonadotropin, "B"	1000 R.U. <i>plus</i> per 100 c.c. serum	Trace	100-500 R.U. per 100 c.c. serum
Estrone	1,000 gamma per 24 hours*	50 gamma (lower limit)	100 gamma
Estriol	100 gamma per 24 hours*	Twice the Estrone	500 gamma
Pregnanediol	3.6 mg. per 24 hours	4-8 mg. per 24 hours	8 mg. per 24 hours at eighth week, increasing to 75 mg. late in pregnancy

*Ratio, estrone to estriol, is almost the reverse of normal.

ovary was seen, as the left had been removed at operation. This remaining right ovary was said to have an atrophic appearance, and no corpus luteum was present.

SUMMARY

A case of chorioepithelioma is presented which followed a left tubal pregnancy, showing almost none of the usual signs and symptoms, and spreading by metastasis to the lungs before it was recognized locally. Hormone assays showed high chorionic gonadotropin and low pregnanediol values.

30 BENNET STREET

PRIMARY OVARIAN PREGNANCY

SOPHIE NOWAKOVSKY, M.D., CHICAGO, ILL.

(From the Women and Children's Hospital)

BECAUSE of the rarity of ovarian pregnancy, particularly of proved cases, the following striking example is reported:

L. S., a white, married housewife, 32 years old, was admitted to the Women's and Children's Hospital on April 15, 1939, to the service of Dr. Giryotas, to whom I am indebted for permission to report this case. The patient complained of pain in both lower quadrants of the abdomen of three weeks' duration.

She began to menstruate at 12 years of age. Periods occurred every twenty-six to twenty-eight days and lasted six to seven days, with heavy flow and slight cramps.

She was married at 24 years of age and had 3 pregnancies. The oldest child was 7 years of age; the youngest 7 months. Lacerations complicated the first pregnancy; forceps were used in the last pregnancy. There was no history of miscarriage or abortion.

The patient had been in good health until Feb. 19, 1939. Following the last pregnancy, her periods were resumed. On Feb. 19, 1939, the patient thought that she was beginning to menstruate; however, this period, instead of ending in a week, continued for over thirty days. At first, bleeding was very profuse. Later it ceased for two or three days and then recurred. Clots were present only on one day.

On March 24, 1939, one day after bleeding stopped, the patient complained of a sharp, shooting pain in both lower quadrants which was so severe that it caused her to remain flexed and quiet. Neither hypodermic injection of morphine nor application of electric pad relieved the pain. There was some relief from use of

shaped, well-defined and demarcated, grayish brown, mushy mass which extended to the serosa without penetrating it. Here, the surface was of a reticulated or irregularly granular appearance. Microscopic examination of this tumor mass, and of all the metastatic masses, showed the same picture observed in the original slide from the biopsy specimen.

Here, then, we have a case of chorioepithelioma that certainly must have developed from the tubal pregnancy removed nine months before the tumor was diagnosed. We get so used to associating chorioepithelioma with hydatidiform mole that we may overlook the fact that fully half of the cases of chorioepithelioma do not follow moles. Here, we have one starting in a tubal pregnancy. If we overlook the possibility of tumor even when there has been no mole, we may lose vital time in making a diagnosis. This tumor, starting in the tubal stump, did not have any thick myometrium to penetrate. It was practically in the peritoneal cavity from the beginning, so its dissemination was rapid. Another point of interest was the fact that lungs so involved with tumor masses should give so few symptoms and signs. The x-ray was taken more or less as a matter of routine, because the patient told of a little cough that had hung on for some weeks. Yet this cough had been so slight that it had not been mentioned until the patient was directly questioned. Even after the x-ray plate, showing massive tumor growths, had been examined, physical percussion and auscultation of the lungs showed astonishingly

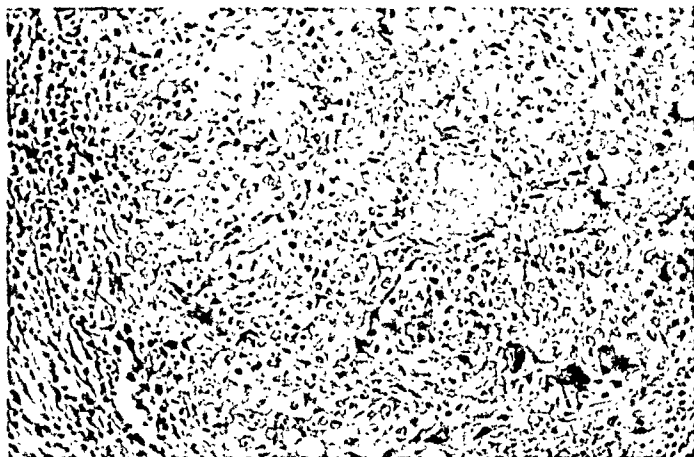


Fig. 2.—Vaginal wall metastasis. Sheets of syncytial cells, giant cells, invasion of vein.

little abnormal change. Yet, at autopsy, it was estimated that at least 50 per cent of the cubic volume of the lungs consisted of tumor tissue. Vaginal bleeding, usually a striking feature in cases of chorioepithelioma, did not appear with this patient. Probably this was due to the fact that the tumor originated near the peritoneal surface of the uterus instead of arising within the uterine cavity, as it more usually does.

Assays of endocrine hormones showed some interesting results. Dr. Werthessen will report more complete findings elsewhere. However, the striking finding from this assay is the enormous quantity of gonadotropic hormone, the luteinizing factor, which was present.

By the method of assay, much of this estrone may be in the form of estradiol.

Any attempt to offer "normal" figures is really inaccurate and unfair. The averages in Table I are presented merely for comparison.

We might expect to find such large amounts of chorionic gonadotropin (B). A more surprising reading is the low pregnanediol. A persisting corpus luteum is almost the rule with hydatidiform mole and with chorioepithelioma. That strong luteinizing influence would lead one to expect a great activity of the lutein cells, with a corresponding high value for the pregnanediol. This condition, however, was not found. In this connection, it may be mentioned that at autopsy only the right

not thickened. The right tube was 6 cm. in length, and revealed no remarkable changes. The appendix was 6.2 cm. in length; the serosa was injected.

Microscopic Findings.—Ovary: Sections taken from the ovary revealed typical findings of primary ovarian pregnancy. The chorionic villi showed varying stages of regressive changes (Fig. 2). There was diffuse recent hemorrhage; necrosis of the ovarian stroma and leucocytic infiltration in the surrounding tissue. Occasional trophoblasts were seen in the vicinity of the blood vessels. In sections examined, no lutein tissue was made out. In certain sections, preserved ovarian stroma formed the external surface. No sections were made through the embryo, as it was desirable to save the specimen intact.

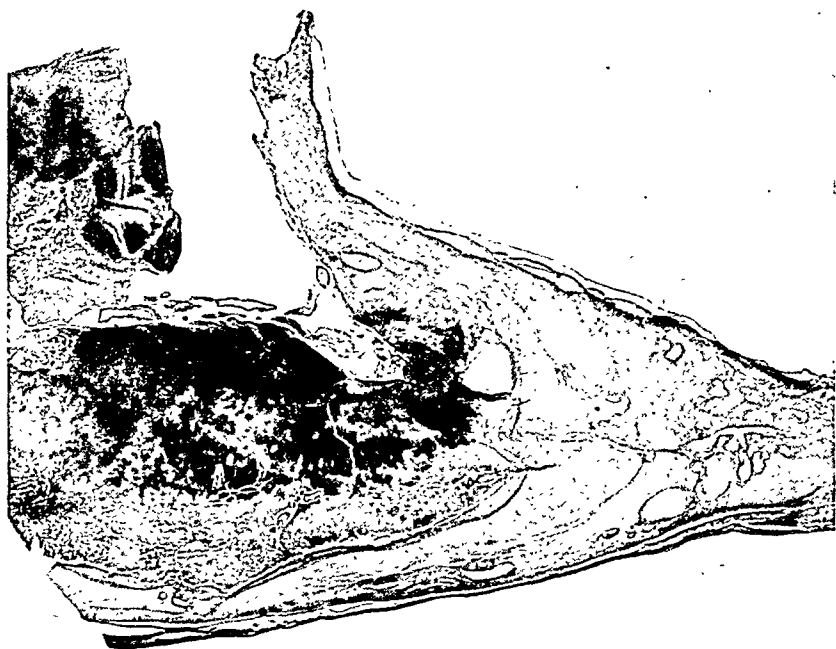


Fig. 2.—Low power of a section through the ovary. Note the outer shell of ovarian stroma, the hemorrhage, and the chorionic villi throughout the section.

Tube: The lumen was free. Tunica propria in some fimbria was slightly thickened. Outer layers showed marked edema with injection of vessels. There was moderate, more focal perivascular infiltration of round cells and plasma cells. A thin layer of fibrin intermixed with red blood cells was present on the serosa. In one site where mesothelium was hyperplastic, there were deposited brown granules, apparently hemosiderin.

Appendix: Foci of lymphocytes and plasma cells were noted around the blood vessels of the serosa and subserosa, presenting a picture of a so-called disproportion periappendicitis due usually to involvement of an adjacent organ.

an ice bag. The pain never fully subsided. It was accompanied by dysuria but not by nausea or vomiting. Before entry to the hospital the pain radiated to the epigastrium.

Physical Examination.—Temperature was 98.4° F.; pulse, 70; respiration, 20.

The patient was a thin white woman, apparently in no great distress. Pupils reacted to light and accommodation. Breasts were atrophic; nipples inverted. Lungs were clear and resonant. The heart rate was regular. Abdominal rigidity and spasm were not elicited. There was marked tenderness above symphysis, more on the right side. The introitus admitted two fingers. Both adnexa were markedly tender. On vaginal examination no masses were felt except for what appeared to be a retroverted uterus. But on rectal examination the "retroverted uterus" was thought to be a distinct mass posterior to and connected with the uterus. The first clinical impression was ruptured ectopic pregnancy.

Operation (Apr. 17, 1939).—The peritoneal cavity contained bloody fluid. Left oophorectomy, bilateral salpingectomy, and appendectomy were carried out. The postoperative course was uneventful. Patient was discharged April 29, 1939.



Fig. 1.—Cut surface of ovary. Note the amniotic sac with the embryo on the left side.

Macroscopic Description of Specimens.—The left ovary measured 7 by 5 by 4 cm. The surface was nodular and showed no evidence of adhesions. A gross rupture through the surface was not seen. The nodules were only slightly elevated. Shining through the capsule were varied colors, ranging from brown to gray. The consistency of the mass was firm except in the midsuperior portion where it was cystic. On section the cystic area revealed itself as a sac which measured 3 by 2.5 cm. on the cut surface. The lining was a thin, blue, glistening, smooth membrane which was irregularly elevated by the underlying wall. The content of the sac consisted of a slight amount of blood-tinged, thin fluid. In addition, the sac contained a small blood clot. Floating in the fluid content was a well-formed embryo about 0.9 cm. in length. The embryo lay in the posterior half of the sac, attached to the inferior wall by a bluish umbilical cord about 1.2 cm. long and less than 1 mm. thick (Fig. 1).

The sac was situated in the ovarian mass 0.5 cm. from the superior surface, 1.2 cm. from the medial, 1.8 from the lateral, and 3 cm. from the inferior surface. The tissue surrounding the sac showed extensive hemorrhages of yellow brown color. In the inferior-medial border of the mass preserved ovarian structure could be discerned, measuring 3 by 1 cm. The attached tube was 5.5 cm. long and 0.5 cm. thick. Its surface was smooth and glistening. The fimbriated end was patent and normal in appearance. The lumen was not distended. It contained no blood. The wall was

Heart: There was hypertrophy of syncytial fibers with a relative increase of the nuclei.

Lungs: There was extensive infiltration of the parenchyma with erythroblastic islands. These were located principally in the sinusoids and periportal spaces, occasionally replacing the liver cells. The cell columns were compressed. Some of the cells showed early vacuolization. Iron stain was strongly positive.

Spleen: There was marked infiltration of red and white pulp by erythroblastic cells with derangement of the normal architecture. No Malpighian corpuscles were seen. Iron stain was positive.

Pancreas: Scattered islands of erythroblastic cells were present.

Adrenals: There were occasional islands of erythroblastic cells in the zona fasciculata.

Kidneys: There were scattered islands of erythroblastic cells in the cortex at the corticomedullary junction with numerous areas of these cells arranged in columns about the interlobular arteries. The tubules contained large deposits of yellow pigment. Parenchyma showed severe cloudy swelling. Iron stain was positive in the tubular area.

Ovary: There were several small blood-forming islands in the central hilum portion.

Bone: Sections of sternum, rib, femur, tibia and humerus showed marked hyperplasia of the marrow with predominance of the cells of the erythroblastic series. There was a lack of development of cortical bone despite the well-formed periosteum.

Brain: Normal tissue except for edema.

Placenta and Cords: The villi were larger than normal, blunt, and presented both a hyperplastic and an edematous stroma. The syncytial cells were large and vesicular with partial persistence of Langhan's layer. There were small islands of hematopoietic activity within the stroma of the hyperplastic villi. The capillaries contained many cells of the erythroblastic series. Wharton's jelly presented a loose edematous alveolar structure.

The body of Baby A was kept in fixing solution for twenty days before autopsy, but, despite this, generalized edema was still apparent, particularly in the eyelids and scalp. There were no gross developmental abnormalities. The abdomen was moderately distended. Inspection of the organs in situ revealed no abnormalities of lungs, liver, spleen, gastrointestinal tract, cardiovascular, biliary, or lymphatic systems or the pelvic organs. The heart and liver were grossly enlarged. A review of the sections showed extramedullary hematopoiesis in the thymus, spleen, pancreas, and kidney, with hyperplastic bone marrow. Iron stains were positive in the liver, spleen, and kidneys.

Taddei, Antonia: Vaginal Lesions From Potassium Permanganate, *Rassegna d'ostet. e ginec.* 49: 61, 1940.

The author describes in detail 2 cases of patients with genital lesions produced by potassium permanganate introduced into the vagina as an abortifacient. He completely reviews the literature on this subject and summarizes in detail the characteristic pathology, symptomatology, differential diagnosis, clinical course, complications, and treatment of this condition.

CLAIR E. FOLSOME.

UNIVERSAL EDEMA OF THE FETUS IN EACH OF MONOCHORIONIC TWINS WITH PATHOLOGIC FINDINGS (ERYTHROBLASTOSIS FETALIS)

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CLEVELAND, OHIO

(From the Department of Obstetrics and Gynecology, Western Reserve University
Medical School, and The Cleveland City Hospital)

LABOR was normal. Twin A was delivered by breech extraction and Twin B by podalic version and breech extraction. Both deliveries were moderately difficult. The babies were females, Twin A weighing 2,891 Gm. and Twin B 3,350 Gm. They were quite similar in appearance, both presenting generalized mild icterus and marked pitting edema of all subcutaneous tissues, particularly over the scalp, neck, and posterior thorax. The abdomen of each baby was greatly distended. In each the liver and spleen could be palpated 6 cm. below the costal margins. The fetal heart beat for five minutes in each baby, but respirations were never established.

The placenta was about twice normal size and very edematous. There were two cords, two amniotic sacs, and one chorion. The circulation of the placenta was that of monovular rather than bivular twins. Both babies died before blood studies could be made.

*Gross Pathology.**—On opening the body of Baby B, a large amount of bile-stained fluid ran from the cut surfaces. The thoracic organs were all present and in normal relationship. Each hemithorax contained 10 c.c. of bile-stained pleural fluid. Lungs were atelectatic, but otherwise heart and lungs were normal.

There were approximately 100 c.c. of bile-stained fluid in the peritoneal cavity. There were no abnormalities of the organs, including the thoracic duct and bile ducts. The liver and spleen were grossly enlarged and firm.

The brain was very friable, but otherwise normal.

TABLE I. TABLE OF COMPARATIVE WEIGHTS

	NORMAL	BABY B	BABY A
Heart	21	36	35
Liver	134	200	145
Spleen	10	27	15
Kidneys (combined)	23	30	24
Brain	363	300	300

The placenta was unusually large and edematous. Two cords were attached. The maternal surface was boggy, variegated gray, yellow and red with the cotyledons prominent. Wharton's jelly was increased and was edematous.

Microscopic Pathology—Review of Sections (Baby B).—

Skin: The stratum corneum presented a loose alveolar structure due to the marked edema.

Breast: The tissue was that of nonlactating breast. The stroma presented extramedullary hematopoiesis.

Skeletal Muscles: The normal architecture was distorted by severe edema.

Thymus: There was a decrease of thymocytes in the cortical lobules for a gland of this development, with marked infiltration of the stroma with erythroblastic islands.

*The general appearance and gross pathology are given only in such detail as to exclude the possibilities of fetal peritonitis, congenital elephantiasis, anomalies of the cardiovascular and biliary systems or of the thoracic duct, disomionphalo-angiopaghic monstrosities and other recognized causes of fetal dropsy.

The patients were of different religious affiliations and of various nationalities. All were white. Their ages ranged from 19 to 36 years. There were no cases in the records of the Boston City Hospital previous to 1936.

SUMMARY AND CONCLUSIONS

There have been 17 cases of vaginal burns from the insertion of potassium permanganate tablets admitted to the Boston City Hospital since 1936. The tablets in all cases were inserted to simulate or stimulate menstruation. Diagnostic points were painless vaginal bleeding following a period of amenorrhea, a tightly closed cervix, and one or two circumscribed charred lesions in the vagina 1 to 3 cm. in diameter. Only one patient miscarried, and she after discharge from the hospital. No connection between the cases could be found.

These cases are readily confused with threatened and incomplete abortion. They emphasize the importance of manual and speculum examination of patients with threatened miscarriages.

A PORTABLE OBSTETRIC DELIVERY TABLE

OTTO H. SCHWARZ, M.D., AND E. F. BRUNING, M.D., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, Washington University)

THE importance of proper position of the patient in home obstetrics is emphasized in the publication *Maternal Care Complication*, edited by Dr. Fred L. Adair, approved by the American Committee on Maternal Welfare, Inc. Quoting from page 88, "The day has gone when those doing obstetrics should be satisfied with the makeshift arrangements accorded them in the past. The patient should be on a table of suitable height and should be properly supported by assistants or mechanical leg holders. She should be properly anesthetized, draped, and in a good light."

Anyone with experience in home obstetrics knows the unreliability of "family assistants" as leg holders, the lack of a suitable table to support the patient and the unsatisfactory results of relying upon the average household to have mechanical equipment suitable for an obstetric delivery. It would be reasonable for a patient to expect that the furnishing of such necessary equipment would be the responsibility of the physician, just as any tradesman is expected to furnish the equipment and tools necessary for his work.

Several years ago, after being unable to find suitable equipment for the securing and maintenance of proper position of the home obstetric patient, the idea was suggested of constructing a portable obstetric table. The problem was more complicated than was anticipated, and we have learned many reasons why suitable equipment had not been developed. Various mechanical devices, clamps, brackets, part tables, full tables, all with numerous modifications were given trial to procure a sturdy, compact, lightweight, portable and economical unit which would assist the physician in providing and maintaining proper position for the "home" obstetric patient.

The unit developed is a table* as illustrated, weight 35 pounds, easily portable, carried in a canvas case. It is fabricated from aluminum and cold rolled steel with chromium plate. The table legs and all working parts can be folded into the hollow interior of the table top in which the Bierhoff leg crutches and hand restraint cuffs are also transported. The table, set up, is sturdy, 21¼ inches wide, 50½ inches long, 36½ inches high. It provides adjustable Bierhoff leg crutches with canvas restraints and canvas hand restraint cuffs. The table can be set up in a few minutes.

This type of table has been used extensively at Washington University, St. Louis, Mo., and the Orange County Maternity Service, Santa Ana, California, and has given satisfactory service.

*The table is manufactured by A. S. Aloe Co., 1819 Olive St., St. Louis, Mo.

VAGINAL BLEEDING FROM POTASSIUM PERMANGANATE BURNS

JOHN C. SHULL, M.D., BOSTON, MASS.

(From the Boston City Hospital)

IN THE years 1936 through 1940 there have been admitted to the Gynecological Service of the Boston City Hospital 17 cases of vaginal bleeding secondary to vaginal or cervical burns from the insertion of potassium permanganate tablets. These cases present a uniform clinical picture which may be easily confused with a threatened or incomplete abortion. Inasmuch as there is no record of similar cases in the literature it has seemed worth while to report them.

Following is the record of a typical case:

Mrs. A. F. (No. 951768), aged 25 years, was admitted at 9 P.M. Sept. 20, 1939. She had had one full-term forceps delivery; she had undergone no operations and had no serious illnesses. Her periods were regular, the last period being June 19. She was admitted with the complaint of profuse vaginal bleeding, passing bright blood and clots. She had experienced no cramps and passed no tissue. She denied attempted induction. Examination revealed a pale nervous young woman in slight shock; blood pressure was 90/54, and pulse 100. General examination was otherwise negative. Pelvic examination showed a parous introitus. The cervix was closed, irregular, and firm. The uterus was that of a six weeks' pregnancy. There were two circumscribed charred areas about 2 cm. in diameter, one on the anterior vaginal wall anterior to and to the left of the cervix and one similar lesion on the posterior vaginal wall just posterior to the cervix. There was a general bloody ooze coming from the anterior lesion. A pack was inserted.

Direct questioning brought the admission that she had inserted a potassium permanganate tablet into the vagina the night before admission.

The hemoglobin was 60 per cent, red count 3.00 million, white count 13,200. The pack was removed in forty-eight hours. She ran a low grade febrile course and was discharged on the sixth hospital day to the prenatal clinic.

On April 14, 1940, A. F. was admitted to the Obstetrical Service in labor and delivered normally a living female, weighing 7 pounds 10 ounces. She had an uneventful convalescence and on the day of discharge a manual and speculum examination revealed no scar nor adhesion which might have resulted from the potassium permanganate burn.

This case exhibits the three characteristics common to all of the 17 cases, namely: painless profuse bleeding; tightly closed cervical os; and a circumscribed, charred vaginal lesion which could be visualized by speculum examination.

While 5 of the 17 women denied using the tablets to induce abortion, 15 had a period of amenorrhea of one day or longer. One of the remaining patients inserted the tablet on the day of the expected period, and the seventeenth patient had a positive Aschheim-Zondek test. It would seem, therefore, that in all the cases the tablet had been inserted to encourage a menstruation.

For treatment six of the patients required only bed rest. Nine were packed for twenty-four to forty-eight hours to stop the bleeding. In two cases the burn had eroded a small artery which required suture. The average hospital stay was five and one-half days.

It was possible to get a follow-up report of 10 of the 17 patients by a search of the out-patient records and by examination of the 6 patients who came to the hospital in response to invitations. Only one patient miscarried two days after discharge from the hospital. Five were not pregnant. Three delivered at term. Two others had positive Aschheim-Zondek tests. Only one patient of 10 had a vaginal-vault adhesion that seemed secondary to the chemical burn.

This table will provide:

1. Proper position for normal delivery.
2. Proper position for episiotomy, version, breech and forceps delivery, and other obstetrical operations.
3. A portable unit for obstetric and gynecologic clinics.

It is not recommended that this table should be used for every home obstetric patient, because there are factors of lack of time, assistants, et cetera which must be considered. However, in many instances these obstacles and disadvantages are not present or can be eliminated by foresight. Even in hospital obstetric practice, emergencies occasionally arise wherein it would be inadvisable and dangerous to insist that without exception, every patient had to be placed on the obstetric delivery table for delivery.

SUMMARY

1. Proper position of the patient is necessary for efficient obstetric care.
2. The practice of obstetrics in the home has been handicapped by the lack of facilities to provide and maintain proper position of the patient during delivery and other obstetric operations.
3. The standards of Class A hospital obstetrics could not be maintained without suitable mechanical equipment.
4. Portable mechanical equipment to provide proper position of the patient can be a valuable aid in eliminating some of the handicaps in home obstetrics, and promote new concepts of safety, comfort, and refinement in the care of the "home" obstetric patient.

Buhmann, Af Arne: The Treatment of Gonorrhea with Sulfapyridine, Ugesk. f. laeger 40: 1159, 1939.

Of 90 cases of gonorrhea treated with sulfapyridine, 26 were in women and 4 in female children. Eleven of the women had received previous treatment with one or two series of sulfanilamide and two of the children had received previous treatment, one with sulfanilamide, the other with estrogen, sulfanilamide, and local applications.

The dosage for the women was 21 Gm. in seven days given in the following manner: 0.5 Gm. 8 times for two days, 0.5 Gm. 6 times for three days, and 0.5 Gm. 4 times for two days. Smears became negative to gonococci in from two to seven days following the beginning of the treatment, except in 2 cases in which the positive smear persisted for eleven and sixteen days, respectively. Twenty-five of the patients were considered cured after a period of observation which averaged eight weeks, but which ranged from two to seventeen weeks and during which an average of 8 negative smears were obtained. The one patient in whom there was a recurrence had received 16.5 Gm. of sulfapyridine in six days and had had a negative smear on the seventh day. On the fourteenth day, a positive smear was obtained and the patient was then lost from observation.

Toxic symptoms noted were headache, vertigo, nausea, vomiting, exanthemas, diarrhea, cyanosis, facial edema, icterus, and acroparesthesia. Only 11 of the 26 patients were free from toxic symptoms during the treatment. Headache, vertigo, and vomiting were the most common of the toxic effects and with the exception of one case of icterus which persisted for three weeks were relatively transient.

The children received a dosage of sulfapyridine which varied from 1/14 to 1/20 Gm. per kilogram of weight a day for from two to seven days. Only one patient had a toxic symptom which was vomiting. Two patients were cured and 2 were not.

CLAUDE J. EHRENBURG.

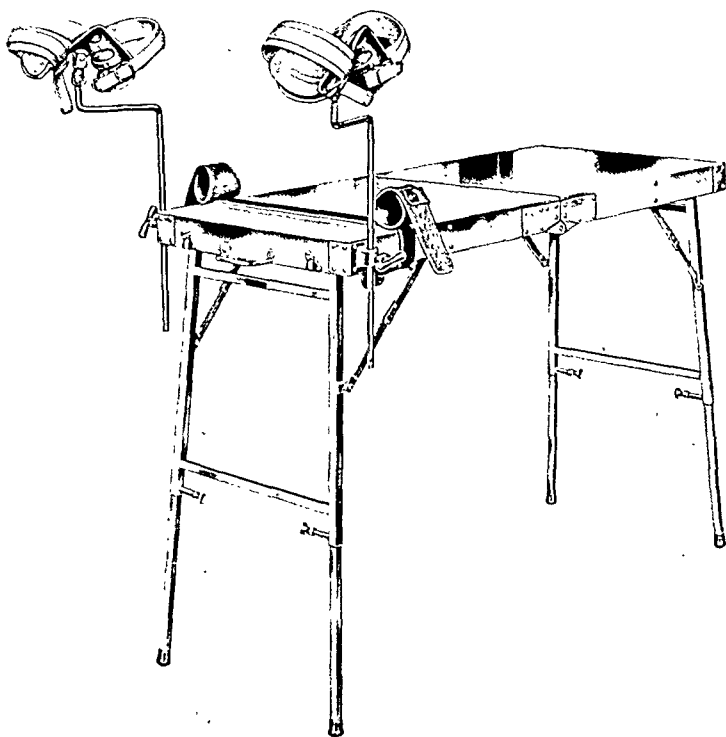


Fig. 1.

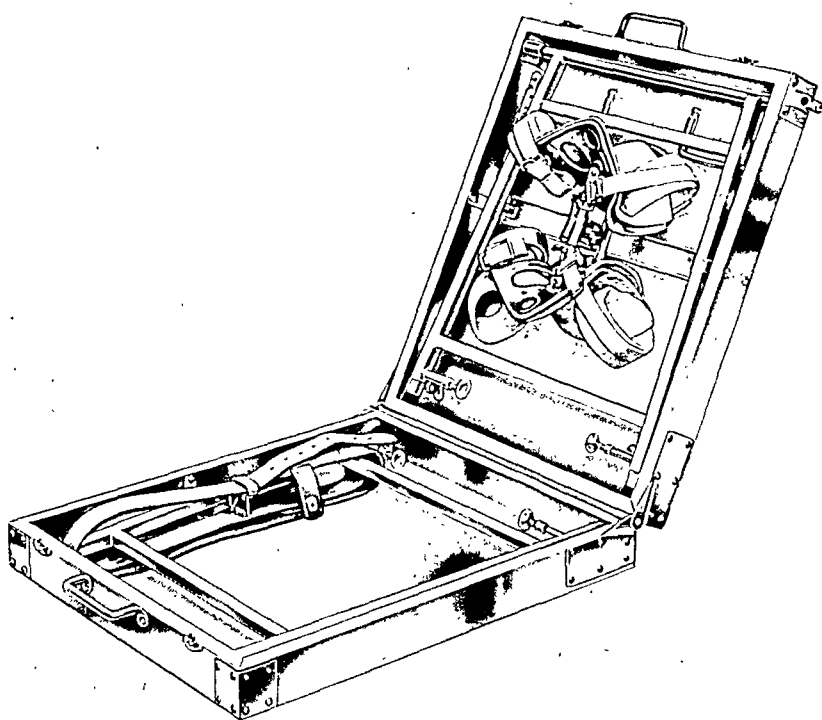


Fig. 2.

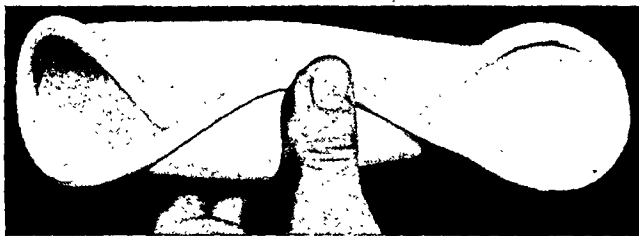


Fig. 2.—Method of holding gynepad when it is to be introduced through a midline incision.

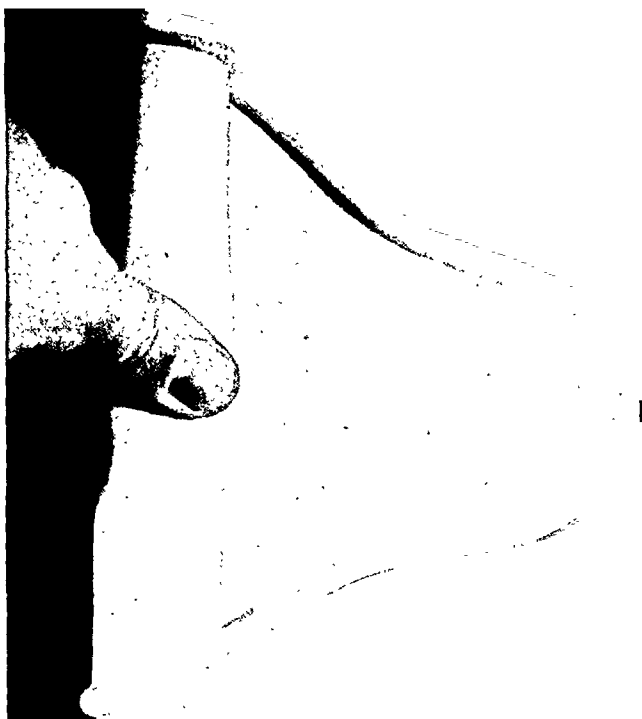


Fig. 3.—Method of rolling gynepad when it is to be introduced through a Pfannenstiel incision.

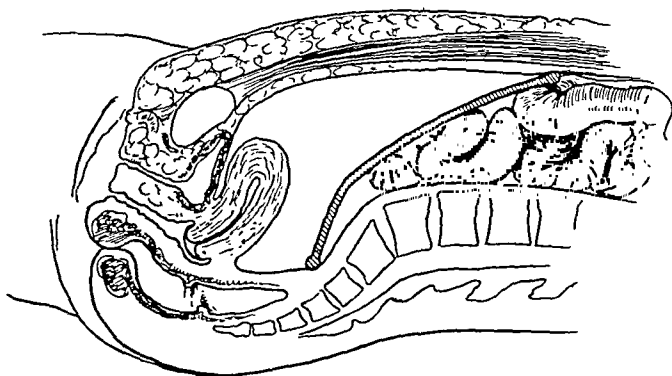


Fig. 4.—Lateral view of gynepad in position.

THE GYNEPAD, A RUBBER DIAPHRAGM TO BE USED IN PLACE OF LAPAROTOMY PADS IN PELVIC SURGERY*

J. RANDOLPH GEPFERT, M.D., NEW YORK, N. Y.

SURGEONS concede that the use of rough cloth pads in pelvic surgery produces considerable peritoneal trauma, with its consequences. Many modified pads have been devised in an attempt to avoid some or all of the inherent disadvantages. Most of these modified pads take the form of a rubberized bag or envelop in which may be inserted a towel or pad to lend body to an otherwise flaccid covering. While all of these combinations have several advantages, most of them still have some of the undesirable features of the cloth pads. For example, it is usually necessary

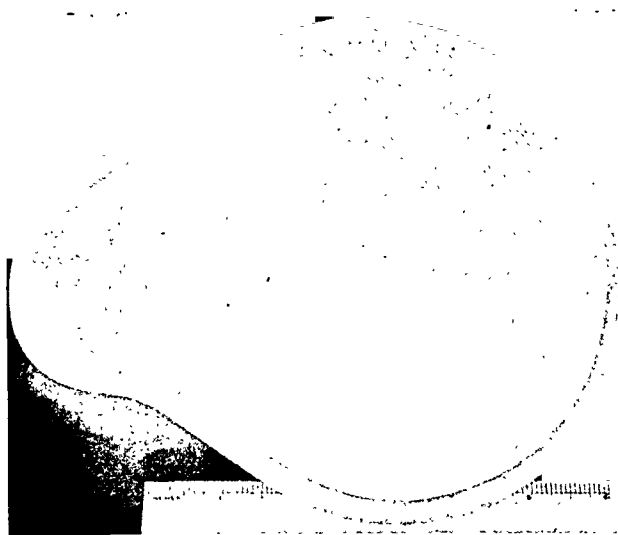


Fig. 1.—Top view of gynepad.

to use two or more of them in the average pelvis, thereby offering more opportunity for prolapse of intestine into the operative field. Also, they form a bulky mass which is difficult to retain in place, and offers little protection against upper abdominal contamination from the pelvis.

The "gynepad" has been designed to overcome these difficulties. It is a molded gum latex rubber diaphragm approximately six inches in diameter (Fig. 1) with a smaller tongue-like projection which is shaped to fit well into the pelvic culdesac. This small projection forms an angle of approximately 130 degrees with the larger surface of the diaphragm, in order to compensate for the promontory of the sacrum. All surfaces are smooth to eliminate trauma. Sufficient rigidity is obtained by having a molded bead about the periphery.

Satisfactory introduction and placement of the "gynepad" may be accomplished in any one of a number of ways. When one is operating through a midline incision, it is easily introduced after being folded longitudinally into three thicknesses (Fig. 2). The upper angle of the incision is lifted with a retractor and the corresponding end of the "gynepad" is introduced into the peritoneal cavity sufficiently to allow the tongue-shaped end of the pad to be placed in the culdesac. The pad is then released and allowed to spread itself over the intestinal mass. When operating

*Presented at a meeting of the New York Obstetrical Society, May 14, 1940.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

The Puerperium

Benedik, A.: The Lochia, *Monatschr. f. Geburtsh. u. Gynäk.* 107: 73, 1938.

One thousand puerperal women were studied to determine the quality and quantity of their lochial discharge. Blood-red lochia often persist longer than eight to ten days. This increased duration of red lochia is not always a sign of any pathologic disturbance. The author maintains that we cannot come to any decisions concerning the degree of involution of the uterus from the color of the lochia alone. If no other contraindications exist, women with red lochia may be permitted out of bed and may be allowed to leave the hospital. The author found that red lochia persist longer in elderly primiparas and in women who do not nurse their babies. Other factors in the determination of the color of the lochia are hypoplasia, frequently repeated pregnancies, persistent fever during the puerperium, prolonged labor and operative deliveries. Elevation of blood pressure is important in determining the color of the lochia only in the cases of pregnancy toxemias. Ergot preparations produce a more rapid disappearance of red lochia.

J. P. GREENHILL

Phillips, Miles H.: The History of the Prevention of Puerperal Fever, *Brit. M. J.* 1: 1, 1938.

The author gives a very comprehensive survey of the history of puerperal sepsis and a review of prophylactic measures, dating from about the middle of the nineteenth century.

The fundamental principle of contagion was suggested by Alexander Hamilton in 1781, demonstrated by Alexander Gordon in 1795, and supported vigorously by Oliver Wendell Holmes in 1843. The author shows that outbreaks of puerperal sepsis in hospitals and localized communities gave impetus to investigative efforts. These have occurred over the entire world.

Leeuwenhoek's discovery of micro-organisms with his primitive microscope, Pasteur's proof that micro-organisms cause disease, and Lister's application of these findings to his aseptic and antiseptic technique are examples of discoveries that have revolutionized surgical technique. Semmelweis in Vienna deserves unlimited credit for his observation of the mode of spread of the dreaded infection from one patient to another.

The discovery of transmission by fomites and subsequent use of masks to prevent transmission of germs from the noses and throats of attendants was another step forward in the war against this disease. Credit for this must go to Hübener, Flügge, Mikulicz, and others. Surgeons were quicker to accept these new discoveries than were obstetricians. The author states that the pioneer in the use of the mask in obstetric practice is Joseph B. DeLee. Scientific support for the theory of air-borne infections from respiratory tracts of attendants finally came, resulting in general acceptance of the use of the mask but only after DeLee had been advocating it for no less than twenty years.

Special recognition is given to the work of Colebrook. Mention is also made of J. Whitridge Williams' calling attention to the possibility of parturient women conveying the organisms on their fingers to the vulva and vagina.

through a Pfannenstiel incision, it may be found advantageous to roll the pad from top to bottom (Fig. 3), introducing first one side and then the other into the peritoneal cavity. The technique of introduction, however, will undoubtedly be modified by each operator to suit himself.

The "gynepad" seems to work best when the patient is maintained in a very slight Trendelenburg position. Since intestinal pressure maintains the pad in close apposition with the lateral and anterior peritoneum, it is not necessary to have the patient in a profound state of anesthesia in order to have a clear operative field. If, for any reason, such as teaching, one prefers an exaggerated Trendelenburg position, then the "gynepad" may be maintained in the pelvis by passing a silk suture through its upper part and fastening this suture to the fascia at the upper angle of the incision.

When properly placed, the "gynepad" divides the peritoneal cavity into two parts (Fig. 4), the upper containing the intestines, and the lower, which is left free for any desired surgical procedure.

Briefly, then, the "gynepad" is a flexible gum rubber pad designed to keep the pelvis free of intestine during a laparotomy. It is incapable of producing peritoneal trauma, is easily introduced and removed, can be repeatedly sterilized by boiling, may be used for long periods of time, and acts as a tight-fitting barrier between the operative field and the remainder of the peritoneal cavity. It is economical, easy to use, and should save considerable time in most pelvic laparotomies.

The "gynepad" may be obtained from The Alco Rubber Company, 1945 Park Avenue, New York, N. Y.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

Meeting of May 14, 1940

The following case report and papers were presented:

Maternal Death Caused by Hemorrhage in the Adrenals. Dr. R. A. MacKenzie.
(For original article, see page 150.)

The Gynepad, a Rubber Diaphragm to Be Used in Place of Laparotomy Pads in Pelvic Surgery. Dr. J. R. Gepfert. (For original article, see page 165.)

An Historical Review of Placenta Previa. Dr. James P. Marr.

Throat swabs taken on 120 medical students prior to work on the maternity wards showed 22.5 per cent had hemolytic streptococci and 4.2 per cent (five students) had the Lancefield Group A strain. Four of these 5 at the time were working on the children's ward. No relationship was noted between the incidence of Group A strain and the presence of tonsillar tissue.

Treatment consisted of moderate outdoor exercise, swabbing, and administration of prontosil. Persistence of positive throat swabs was noticeable in those whose nasopharynx was in an unsatisfactory condition.

FRED L. ADAIR AND J. R. KIGHT,

Cosgrove, S. A., and Barry, Thomas A.: Antepartum Gas-Bacillus Infection, New England J. Med. 222: 344, 1940.

The authors describe a case of ante-partum infection with *Clostridium welchii* leading to infection of the fetus by way of placenta and resulting in a stillbirth. Under serum treatment supplemented by sulfanilamide the patient had an uneventful post-partum course except for an afternoon temperature rise up to 101° F.

From study of the literature the writers conclude that the *Clostridium welchii* will not by itself cause damage unless the conditions are suitable. As the liberated toxins devitalize more tissue the infection progresses. The uterus is a perfect incubator and the dead fetus an excellent medium for growth. Since there is no way of telling that the dead fetus is infected, one is forced to await the outcome of delivery before making a diagnosis. Surgery has no definite place in the therapy, forcing the obstetrician to be conservative. Sulfanilamide seems of value.

HUGO EHRENFEST

Delmas, P., and de Kereau, J. C.: Attempts at Prophylaxis of Puerperal Infection by Means of Sulfamides, Bull. Soc. d'obst. et de gynéc. 27: 711, 1938.

A series of 493 puerperal women were given sulfanilamide as soon after delivery as possible and for at least four days afterwards. The authors observed that following this prophylactic therapy there was a slight decrease in mortality and a considerable reduction in morbidity. The reductions were sufficient to justify continued use of this prophylactic medication.

J. P. GREENHILL

Schäfer, Gunther: A Study of the Bactericidal Power of the Blood After Chemotherapeutic Prophylaxis During Pregnancy and Puerperium, Deutsche med. Wchnschr. 66: 240, 1940.

Using cultures of hemolytic streptococcus, Schäfer was able to do 187 tests on the blood of 125 women who were divided into three groups: untreated, taurolin-treated and prontosil-treated. Blood samples, taken at various intervals during pregnancy and the puerperium, were inoculated with fresh cultures in a dilution of 1/10,000 and incubated for three to six hours, then poured on sterile plates. The criterion of the effect on virulence was taken from the effect on the appearance and count of colonies.

In untreated cases a diminution of bacterial virulence was found in the first and second halves of pregnancy. During the event of labor, virulence increases, remaining at a high point until the fifth to seventh day post partum, when a temporary increase in natural bactericidal power was shown. From the seventh day the virulence was shown to be increased. The taurolin- and prontosil-treated cases showed a definite increase in bactericidal power during pregnancy, labor, and puerperium. In operative deliveries no significant variation in effect on bactericidal power was noted. The author attempts to provide a bacteriologic guidepost for chemotherapy in pregnancy. Dosages of taurolin and prontosil are not given.

R. J. WEISSMAN

After a review of modern air conditioning and treatment of air with ultra-violet light, the author concludes with the statement that the most complete surgical technique is essential in really safe obstetric practice.

F. L. ADAIR AND JOHN A. HAUGEN

Theron, R.: Puerperal Sepsis at Home and in Hospital, South African M. J. 12: 9, 1938.

Since in England, as well as in many other countries, there has been no decrease in the death rate from puerperal sepsis during the last twenty years, the author had decided to review the situation and to make comparisons between home and hospital deliveries. A history of our knowledge of puerperal sepsis and its etiology is given. Semmelweis' epochal discovery in 1847, with Pasteur's and Lister's discoveries later, marks the beginning of modern concepts of the disease.

The author states that the present death rate from puerperal sepsis in England is 1.7 per 1,000 live births, as compared with 1.42 twenty years ago. The apparent retrogression rather than improvement may be due to a changing basis for death certification and also changes in the classification for statistical purposes. However, the advances in the antenatal care and in general welfare work of recent times make the comparative results all the more disappointing.

A review of the bacteriology is given. The list of causative agents includes streptococci (hemolytic and nonhemolytic) (aerobic and anaerobic), *S. viridans*, *Staphylococcus aureus* and *albus*, pneumococcus, gonococcus, *Bacillus welchii*, and others. He lists all abnormalities of labor which cause prolongation of labor, excessive trauma to the soft tissues, hemorrhages, and instrumental deliveries (except simple low forceps operations conducted in ideal surroundings) as predisposing causes of infection. Eighty to ninety per cent of all cases are due to some type of streptococcus. Also he adds that the nonhemolytic strain can be found in the vaginas of nearly all women before labor, but the hemolytic variety can rarely be found in healthy women and is commonly found in infected cases, both in the uterus and in the blood. Anaerobic streptococci can be found in the genital tract of pregnant women and women in labor and rank second only to the hemolytic streptococcus as a causative agent in puerperal infection.

The author theorizes that the hemolytic streptococci are probably always conveyed to the genital tract extrinsically, either by droplet or by the hand or instrument of an attendant. Also the curve of incidence of puerperal morbidity follows fairly closely the seasonal curve of incidence of influenza and colds.

Resistance of the patient and also vitamin deficiency are discussed in connection with the etiology.

The discussion of treatment is dismissed with a few words on general supportive measures. Prevention implies ensuring the health of our expectant mothers plus early recognition of conditions of a mechanical nature, such as contracted pelvis.

A rigid technique as regards asepsis will do much to lower the present morbidity. Antiseptics too are steadily being improved. The author reviews Colebrook's work on the efficiency of various antiseptics.

In conclusion, he summarizes that comparative figures for home and hospital practice are unfair, because the complicated cases are always moved to a hospital and the simple cases are left in the home. Home delivery services should be under the supervision of institutions. Institutions should guard against unnecessary interference with normal cases, adhere to strict isolation of infected cases, and have rigid rules for technique in asepsis and antisepsis. The result should be a lowering of morbidity and mortality rates.

F. L. ADAIR AND JOHN A. HAUGEN

Fleming, Amy M.: Puerperal Sepsis and Haemolytic Streptococci, Brit. M. J. 2: 639, 1939.

It was estimated that not less than 85 per cent of fatal infections following normal deliveries in England in 1932 were due to hemolytic streptococci. Lancefield and Hare later showed that almost all the infecting strains in severe puerperal sepsis belonged to Group A hemolytic streptococci.

In severe puerperal infections of the genital tract whatever their etiology, sulfanilamide may be used and should be, provided the patient is in a hospital where its administration may be controlled.

WILLIAM C. HENSKE.

Bonafos: The Treatment of Puerperal Infection With Sulfamide Derivatives, Bull. Soc. d'obst. et gynéc. 28: 344, 1939.

The author reports a series of 60 cases of puerperal infection treated with sulfamide derivatives. He believes that these drugs will play a very important role in the battle against these infections not only as a prophylactic but also as a curative measure. For the purpose of overcoming an already existing infection, the drugs must be given judiciously, early, and when there are not localized or diffuse suppurations which require surgical interference. Care, however, must be exercised in the use of these drugs. Necessary precautions are: avoidance of sulfates, absolute rest in bed, and the use of sodium bicarbonate.

J. P. GREENHILL.

Gayus, Greene-Armytage, and Baker: Puerperal Agranulocytosis Following Sulphanilamide Treatment, Brit. M. J. 2: 560, 1939.

A fatal case of puerperal agranulocytosis following sulfanilamide therapy is reported. It clearly demonstrates the value of frequent blood studies, and points to the possibility of a serious and perhaps fatal upset of the hematopoietic system from sulfanilamide therapy.

FRED L. ADAIR AND JOHN R. KIGHT.

Keller, R., and Limpach, J.: Blood Transfusion in Generalized Puerperal Infection, Rev. franç. de gynéc. et d'obst. 34: 129, 1939.

In the opinion of the authors blood transfusion has a favorable effect in cases of generalized puerperal infection. This is manifested by a sudden fall in temperature and pulse rate, by a suppression of chills and by improvement in the general condition. The earlier the transfusion is given the better the result. To obtain the best results the blood must be given as soon as the infection becomes generalized. Furthermore, the transfusions must be repeated at five- to eight-day intervals. They are useless when given late, particularly if there are metastases and serious septic lesions in important organs.

Contraindications to the use of blood transfusions are endocarditis, nephritis, hepatitis, and acute pulmonary infections. Generally only between 150 and 200 c.c. of blood should be given at one time. The authors used citrated blood, unmixed blood, and placental blood, and they observed no apparent differences.

The authors believe that there is no doubt about the great value of blood transfusions and that this therapy is the best we possess today to combat generalized puerperal infection.

J. P. GREENHILL.

Ramos, Alberto P., and Montes, Alberto A.: Slow Hyper-Arseno-Transfusion (Drop by Drop), as Treatment of Grave Puerperal Infection, Presse méd. 48: 530, 1940.

The authors modified Tzanch's "Massive Arsenotherapy" treatment described for use in seriously ill puerperal sepsis cases. Other authors have utilized serum, physiologic saline, or glucose solutions as diluents for administration of an arsenical in massive arsenotherapy. Ramos and Montes administer the arsenical in the vehicle of a small transfusion of weakly citrated blood. The authors designate their treatment as "slow hyper-arseno-transfusion." This phrase clearly implies the therapeutic action they wish to accomplish.

The technique used is described as follows: 150 cg. of neosalvarsan, diluted in 3 or 4 c.c. of glucose solution, is added to 200 c.c. of weakly citrated (20 c.c. of 2 per cent citrate solution) blood. The hyper-arseno-transfusion fluid is placed

Baird, D., Michie, A., and MacDonald, R.: Prevention and Treatment of Puerperal Sepsis, *Lancet* 2: 148, 1939.

After a study of puerperal sepsis in the city and county of Aberdeen, Scotland, the authors feel that the following conclusions are justified. In a well-run maternity unit, where strict control of all contacts during labor and the puerperium is obtainable, the incidence of streptococcal sepsis can be reduced to a very low level. This incidence depends on the presence of the organism in the genital tract during labor, the patients' resistance, and the amount of trauma sustained. Most of the deaths from such sepsis are caused by the hemolytic streptococcus Group A, absent from the genital tract before labor. The access of the organism to the genital tract can be prevented by asepsis, antisepsis, the use of masks, and the exclusion of carriers of streptococci from the labor room. The risk of infection is much less when the entire labor is conducted in the hospital.

The maternal deaths in Aberdeen are analyzed in two periods: 1931 to 1935 and 1936 to 1938 which are before and after the introduction of sulfanilamide therapy. There was a fall in death rate from 6.2 to 4.6 per thousand due mainly to a fall in the death rate from sepsis from 2.05 to 1.02 per thousand. An analysis of the cases of puerperal sepsis during these two periods shows a fall in the total case mortality from 13.9 to 9.0 per cent and a fall from 19.2 to 8.3 per cent in the case mortality of sepsis due to the hemolytic streptococcus.

It was found that with easy delivery the case mortality in puerperal infection was 12.7 per cent before the introduction of sulfanilamide therapy and 4.1 per cent after. With difficult delivery, the mortality was 28.9 per cent before and 12.8 per cent after sulfanilamide introduction. In spite of sulfanilamide therapy, therefore, the prognosis is poor in hemolytic streptococcal infection in the presence of extensive local trauma.

CARL P. HUBER

Gordon, Charles A., and Rosenthal, Alexander H.: Sulfanilamide Therapy in Severe Puerperal Infection, *Surg. Gynec. Obst.* 69: 631, 1939.

Large doses of sulfanilamide were given to 118 patients with severe puerperal infections of the genital tract, regardless of their etiology. Clinical response was prompt and satisfactory in 45 cases, or 38 per cent. In an additional 45 cases, or 38 per cent, results were not convincing, yet good enough to deduce that the drug may have played an important part in recovery. In 23 cases, or 20 per cent, no beneficial results were observed. There were 5 deaths, a mortality of 4 per cent.

Administration is definitely associated with toxic manifestations, none of which need be a serious hazard. Usually obvious and rarely severe enough to warrant discontinuance of therapy, toxicity is actually low. A moderate fall in hemoglobin is common and harmless. No case of agranulocytosis was seen. Acute hemolytic anemia cannot be foreseen or prevented since it is apparently due to idiosyncrasy, developing quickly within the first few days of treatment after comparatively small doses of the drug. Rapid drop in hemoglobin and erythrocytes, leucocytosis, marked reticulocytosis, bilirubinemia, and urobilinuria are noted. Daily blood counts for at least the first five days are essential. Though it occurs but seldom, and transfusion is effective, it is because of the ever present danger of serious blood changes that indiscriminate administration of sulfanilamide is inadvisable.

In mild cases of puerperal infection, sulfanilamide is not indicated. Certainly proper bacteriologic investigation should precede therapy, but it is not essential. Intrapartum infections should be treated with sulfanilamide at once. Report on *Streptococcus hemolyticus* may be had in twenty-four hours; vaginal swab culture is better than intrauterine. If hemolytic streptococci are found, drug therapy should be discontinued only under exceptional circumstances, and one should not be too quick to stop its administration because bacteria have disappeared or a diagnosis of drug fever has been made.

The most recent experience indicates that optimum benefit may be expected with spaced maintenance doses of 20 to 30 gr. of sulfanilamide and moderate fluid restriction, provided a large initial dose has been given the patient.

cases. In certain other cases there seems to be some abnormality in the innervation of the uterus which results in abnormal contraction of the uterine muscle fibers and the production of inert areas or softening of the uterine wall. Mortality in these cases is high (40 per cent, Cooke). Hemorrhage and shock remain the most important clinical signs. It is to be differentiated chiefly from a prolapsed submucous fibroid. Treatment varies from immediate replacement of the inverted uterus to deferring replacement until after recovery from the shock. The authors advise replacement by gentle taxis associated with active antishock treatment. The cervix may be relaxed by injection of adrenalin (1:1000). In a total of 13 patients treated this way, the authors had 11 recoveries and 2 deaths. Where the cervix is tightly constricted, either the Küstner or Spinelli operation is indicated. Cesarean section is indicated in subsequent pregnancies if inversion had been treated by a surgical procedure.

WILLIAM BERMAN.

Correspondence

Contraceptive Practice

To the Editor:

Having read with keen interest your thoughtful paper, "Contraceptive Practices," in the Anniversary Number (October, 1940) of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, we wish to thank you for it, and at the same time to draw your attention and that of your readers to some wrong impressions which certain of its passages may tend to create.

On page 653, in speaking of "the so-called 'clinics' "—(correctly so termed)—"which are accessible to the general public," you state that it is in these "that reform is necessary." Your reason appears to be that, because many of these centers are not connected with established hospitals, they "are operating usually without the pale of the law . . . and, therefore, uncontrolled by any supervising authority except the local policeman." Clinics approved by the Birth Control Federation of America are operated in full accordance with authentic interpretations of state and federal law.

A recent report on birth control centers in the United States* points out that at the close of 1939, 549 centers were functioning *under medical direction* in 42 states. This direction is by licensed physicians such as those serving in hospital clinics, in many cases the same physicians. They are members in good standing of their medical societies. Such centers cannot, therefore, be described as "uncontrolled by any supervising authority except the local policeman," unless the physicians in charge may be said to function as policemen.

We wholly concur in your hope that in the near future all hospitals will install contraceptive clinics, following such leads as that of Albany Hospital and Strong Memorial in New York State, of Johns Hopkins in Baltimore, The University of California Hospital, San Francisco, and about one hundred others. We need not re-emphasize to you the difficulties and opposition which must be overcome before this goal is reached. Should not effort to achieve it be part of the work of the liberal, civic-minded obstetrician, who is concerned not only with the management of pregnancy, but also with the occurrence of it under favorable, and not under unfavorable, conditions?

The fact that such clinics are needed for those whom you designate as the "medically indigent"—persons who tend to become civically indigent by lack of advice to protect against undesired or contra-indicated overproductiveness of children—is indicated in the above-mentioned Journal of the American Medical Association report. This showed that 34 per cent of new patients in a total of 46,582 were on relief or unemployed, and 60.5 per cent of the total were advised and given materials either without charge or for a fee of one dollar or less.

*Dickinson, R. L. and Morris, W. E.: Birth Control Centers: Report of 202 in U. S. for the year 1939, J. A. M. A. 115: 591, 1940.

in a transfusion bottle, elevated 160 cm. and allowed to *drip slowly* into the vein during the next three to three and one-half hours. The rate of flow is about 20 drops a minute. It is wise to avoid chilling of the blood.

To protect the hepatic function the authors inject at the end of the transfusion, via the same intravenous needle, 50 to 80 c.c. of hypertonic glucose. Immediately after the intravenous hypertonic glucose, 10 cg. of vitamin C and whole liver extract are given intramuscularly. Cardiazol, epinephrine, etc., are used as necessary preliminary medications.

Six abstracted cases are presented, five of these illustrated by reduced graphic sheets. The one fatal outcome was due to an infectious endocarditis; it was the only one of the 6 cases with a positive blood culture.

The reactions to the treatment were adjudged not to be severe. One patient collapsed upon initiation of the treatment but was quickly aroused with stimulants. Transitory anuria was treated in one case. Mild icterus and bronzing (characteristic of saturation) and mild diarrhea were the only other reactionary symptoms.

The authors gave a total of 2 "slow hyper-arseno-transfusions" one a day for two days, to each of three patients. The temperature and pulse in most instances rapidly fell to normal. They note that it has never been necessary to give a third "slow hyper-arseno-transfusion," for beneficial results are obtained after the first or immediately after the second transfusion.

CLAIR E. FOLSOME.

Barr, John B.: The Remote Effects of Puerperal Sepsis, Brit. M. J. 1: 1132, 1939.

In an attempt to determine the remote effects, the author examined 200 patients who had had puerperal sepsis four to six years previously. The examination consisted of the patient's medical and obstetric history before and after the puerperal illness, a general medical, and pelvic examination, including bacteriologic study of the upper vaginal secretion, and a radiologic examination when necessary.

The author found sterility in 77 patients (38.5 per cent), although in 33 (16.5 per cent) this condition may have been due to the use of contraceptives. A noteworthy feature was the increased tendency of abortion, the abortion to labor ratio being 1 to 5.7 before sepsis and 1 to 2.8 afterwards. Also there was an incidence of subsequent sepsis, being 58 per thousand in the patients with sepsis (corrected by author to 39 per 1,000) as compared to 25.1 in an unselected group. As to the general health, a thing difficult to assess was the fact that only 38 per cent had suffered in any way severely.

Gynecologic examinations revealed lesions in 78 per cent of the patients. A total of 237 lesions were found of which chronic cervicitis constituted 57 per cent, chronic corporeal infection 24.4 per cent, chronic pelvic cellulitis 60 per cent, and chronic salpingo-oophoritis 12.6 per cent. Extragenital lesions included persistent phlegmasia in 21 cases.

In the majority of the patients the original organism was the *Strep. hemolyticus*, but in no instance did the present bacteriologic study demonstrate this organism in the vagina.

FRED L. ADAIR AND JOHN NEWDORP.

Harer, W. Benson, and Sharkey, John A.: Acute Inversion of the Puerperal Uterus, J. A. M. A. 114: 2289, 1940.

The authors report one instance of acute inversion of the puerperal uterus seen in 16,240 obstetric cases. They review the chief causes of inversion of the uterus. Suprafundal pressure is mentioned as the most frequent cause of the acute inversion. Mention is made of the causal factors in spontaneous inversion of the uterus, such as increased intra-abdominal pressure brought about by sneezing, coughing, and vomiting. Another theory has been advanced that there is abnormal distribution of the muscle fibers of the fundal portion of the uterus with a preponderance of the circular fibers over the longitudinal ones in some of these

Moreover the statement in the letter that "clinics approved by the Birth Control Federation of America are operated in full accordance with authentic interpretations of state and federal laws," is entirely meaningless. This organization is a self-constituted group of interested individuals; it operates without authority and largely by favor, and while its clinics may be served by medical personnel in good standing, my contention still holds that such activities are uncontrolled by any supervising governmental authority. If those official bodies entrusted with such authority have not acted to assert it, this is a matter not for me to discuss. Incidentally it would be of interest to know how many centers operate outside of the 549 under medical direction or how competent this medical direction may be.

It is admitted in the above letter that "state laws, where they are restrictive, constitute the only barrier" ostensibly, to the operation of the extramural clinics. This would seem to confirm the contention that they are conducted illegally, using the term in a broad sense. However, academic discussions are hopeless in so far as achieving progress in the solution of this troublesome problem is concerned. It is generally accepted that there are definite medical indications which call for methods to avoid conception; possibly these should be extended to include certain social and economic situations if important from the medical viewpoint. If so, why not legalize this activity, through the medium of professional organization?

I do not feel that I have created any false impressions in my article. Until the dissemination of contraceptive advice through clinical facilities can be placed on a basis acceptable to the profession as well as to legally constituted authorities, we must look for further objections to the present scheme. All public dispensary facilities, no matter what their particular field of activity, should operate on the same plane of official supervision and control, and to stress this aim I consider to be one of the main purposes of my article. If this is unattainable, a discussion of pertinent facts does not appear to be out of place. It is only by this means that the abuses which have developed may be adequately handled and eliminated.

George W. Kosmak, M.D.

New York, December 15, 1940.

Item

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Cleveland, Ohio, from May 28 to June 2, 1941, immediately prior to the opening of the annual meeting of the American Medical Association.

Application for admission to Group A (Part II) examinations must be on file in the Secretary's Office not later than March 1, 1941.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reexamination* in Part II must make written application to the Secretary's Office before April 15, 1941.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

In your article, you infer on page 654 that if public health departments include contraceptive service, such activities are in conflict with "established Federal Statutes." Again allow us to correct you. The Federal Statutes on contraception apply only to distribution and importation of books and materials by mail or common carrier. They have been interpreted in the case of *U. S. vs. One Package*, 86F 2nd 737 (C. C. A. 2nd 1936) in the words of the decision. "Not to prevent the importation, sale, or carriage by mail of things which might intelligently be employed by conscientious and competent physicians for the purpose of saving life or promoting the well-being of their patients."

You may recall that this case was not taken by the Government to the United States Supreme Court for review because the U. S. Attorney General accepted this decision as law. It is, in consequence, definitive. The Federal Law, therefore, has no bearing on activities of a state public health department in providing contraceptive service.

The state laws, where they are restrictive, constitute the only barrier; otherwise the right of the physician to prescribe contraceptives for the patient has been unchallenged. In two states, Connecticut and Massachusetts, state laws have been construed by the courts as prohibiting physicians from advising on contraception. These laws state respectively that the use of a contraceptive is illegal, and that *offer or issuance* of a contraceptive is illegal. Curiously, medically indicated abortion and sterilization are legal in both states!

Your article contains so much that is helpful, sound and constructive that we regret the inclusion in it of any statement which is not in harmony with facts. Knowing that you would not wish to create a false impression, we are sending these corrections, and trust that they will receive early publication and prominence comparable to that of your excellent article.

Richard N. Pierson, M.D.

Robert L. Dickinson, M.D.

Ira S. Wile, M.D.

Woodbridge E. Morris, M.D.

Representing the Birth Control Federation of America.

New York, December 28, 1940.

A Reply

The foregoing letter is answered herewith by the undersigned as an individual, not as an editor of the JOURNAL. What I have to say therefore has no official implications in so far as this publication is concerned.

To begin with, I do not feel that I have erred in stating that most of the extramural clinics, namely those not connected with established hospitals, which exist for the public dissemination of contraceptive information, are operated without the pale of the law. The question of their supplying a demand for such services, is not under consideration. However, to the best of my knowledge, these particular clinics, sponsored by the Birth Control Federation of America, are not licensed by any constituted authority and therefore are not subjected to official control, regulation, or inspection, such as is imposed upon established dispensaries.

I repeat that I do not refer to those contraceptive clinics which are part and parcel of a hospital service but to those of definitely extramural character in which little distinction is drawn, in most instances, between perhaps questionable social and definite medical indications. It is here, I believe, that abuses can and do arise, a fact to which many physicians can testify. Not only the indigent but many other women freely patronize these readily accessible facilities in response to a widespread propaganda backed apparently by unlimited funds. The *Journal of the American Medical Association*, quoted by the protestants, shows that only 34 per cent of the treated patients come definitely into the indigent group, that 60 per cent of the total were given advice and treatment without any, or for a nominal charge (i.e., they were considered indigent), which still leaves about 40 per cent who, as a matter of fact, should not have been accepted under the common dispensary laws.

- New England Obstetrical and Gynecological Society.** *President*, Frederick L. Good. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** *President*, John Vruwink. *President-Elect*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson. Next meeting, Los Angeles, Calif., November 5 to 8, 1941.
- Washington Gynecological Society.** *President*, R. L. Sylvester. *Secretary*, W. R. Thomas, 1830 K. Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, E. L. Zander. *Secretary*, Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, E. Lee Dorsett. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Henshaw Kelly. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, Roy Grogan. *Secretary*, J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Galveston, Texas, September, 1941.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, Russell W. Allen. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Francis R. Irving. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, T. M. Boulware, Birmingham, Ala. *Secretary*, Eva F. Dodge, 519 Dexter Avenue, Montgomery, Ala. Next meeting, Mobile, Ala., April, 1941.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.

Books Received

L. EMMETT HOLT. *Pioneer of Children's Century.* By R. L. Duffus and L. Emmett Holt, Jr. Foreword by Edwards A. Park, Professor of Pediatrics, Johns Hopkins University. Illustrated. 295 pages. D. Appleton-Century Company, New York, 1940.

MULTIPLE HUMAN BIRTHS. By Horatio Hackett Newman, Ph.D., Sc.D., Professor of Zoology, University of Chicago. Illustrated, 214 pages. Doubleday, Doran & Co., New York, 1940.

FOREIGN BODIES LEFT IN THE ABDOMEN. The Surgical Problems and Legal Problems. By Harry Sturgeon Crossen, M.D., School of Medicine, Washington University, and David Frederic Crossen, LL.B., School of Law, Washington University, St. Louis. With 212 illustrations, including 4 color plates, 762 pages. The C. V. Mosby Company, St. Louis, 1940.

DISEASES AFFECTING THE VULVA. By Elizabeth Hunt, M.D., Ch.B. (Liverp.), Honorary Physician to the Skin Department, South London Hospital for Women, etc. With 36 illustrations and 18 plates in color. The C. V. Mosby Company, St. Louis, 1940.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(*Appears in January, April, July, October*)

- American Gynecological Society.** *President*, E. J. Litzenberg. *Secretary*, Richard W. TeLinde, 11 East Chase Street, Baltimore, Md. Next meeting, May 26 to 28, 1941, Broadmoor Hotel, Colorado Springs, Colo.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, Frederick H. Falls, Chicago, Ill. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting will be held at the Homestead, Hot Springs, Va., September 11 to 13, 1941.
- Central Association of Obstetricians and Gynecologists.** *President*, Thomas B. Sellers, New Orleans, La. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Next meeting, New Orleans, La., Fall of 1941.
- South Atlantic Association of Obstetricians and Gynecologists.** *President*, M. P. Rucker, Richmond, Va. *Secretary*, Robert A. Ross, Durham, N. C. Next meeting, February 7 and 8, 1941, Jacksonville, Fla.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Norman F. Miller, Ann Arbor, Mich. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June 2 to 6, 1941, Cleveland, Ohio.
- New York Obstetrical Society.** *President*, Thomas C. Peightal. *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** *President*, Roy W. Mohler. *Secretary*, John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** *President*, Harold K. Gibson. *Secretary*, James A. Gough, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** *President*, George G. Cochran. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** *President*, Abraham Samuels, *Secretary-Treasurer*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society.** *President*, E. W.ENZ. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Esther C. Wallner. *Secretary*, Samuel S. Gordon, 520 Heyburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** *President*, S. A. Chalfant. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** *President*, Raymond S. Titus. *Secretary*, Judson A. Smith, 262 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

thorough investigative study, no gross pathologic changes are revealed as possible precipitating factors. To restrict this widely used term within such narrow limits means the probable overlapping of factors, for the separation of an anatomic lesion from a functional disorder, is not possible in every case. While the uterus is the final source of the bleeding and the ovaries directly control the function of the uterus, it is required that the thorough examination include the entire body, the environment, the habits, and complete laboratory investigations. Bleeding due to myomas, polyps, pelvic inflammatory disease, or gestational states obviously is not functional in type. Nor can demonstrable constitutional affections, such as anemia, cardiac diseases, nutritional upsets, and other general disorders that are frequently associated with abnormal bleeding from the uterus, be interpreted as functional.

In this review we offer no new classification, as the present nomenclature is too firmly imbedded in the medical indices. The second reason for not submitting a new system of classification is that we feel the present tendency of each investigator to apply his own terminology has done much to becloud the minds of the medical profession. The third reason is the inadvisability of applying inadequate terms to conditions and changes not fully understood.

Impressed by the marked frequency with which the diagnosis of functional bleeding is made in the presence of demonstrable gross pathology, we have collected a series of cases in which the primary complaint was "abnormal uterine bleeding." The series is large enough to permit conclusions, without recourse to other works. Our interpretations are based entirely on our clinicopathologic findings, and the human element must be considered in this report. The complaint of abnormal bleeding is probably the most frequent symptom which the gynecologist is called upon to treat. The treatment of this symptom without an honest attempt to determine the cause, and resorting to the use of therapeutic agents because of their glamour appeal to the patient and the doctor, has led us to accept the term "buttockal syndrome," which includes those patients who receive their routine injections of minerals, drugs, and hormones "per gluteum" without rhyme or reason. Fortunately the potency of most of the accepted agents is so low as not to constitute a potential danger to the future welfare of the patient. Certainly the prolonged course of therapy is not only a drain on the financial status of the patient, but will in time undermine the patient-doctor relationship.

Because of the frequency of endocrinopathies in early adolescence and during the climacteric, our cases have been limited to those patients in the third and fourth decades of life. The complaint of pain, the fear of cancer, or the admission of possible pregnancy has removed the patient from this series. Though some hold that certain constitutional types are prone to menstrual aberrations, we have found no evidence in our series to support this; a more correct deduction would probably have been obtained if the investigators had delved more deeply into the patient's history and habits. To speculate concerning the unknown is usually entertaining but certainly profitless to the clinician; expensive

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A CLINICOPATHOLOGIC INVESTIGATION OF THE CAUSES OF MENOMETRORRHAGIA

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NOTWITHSTANDING the tremendous advances made in our knowledge of the activities of the female genital tract, the fundamental causes of either normal or abnormal bleeding are still not fully understood. With the advent of fashionable organotherapy into the therapeutic armamentarium of the gynecologist, a voluminous literature has accrued, tending to make the evaluation of the innumerable forms of therapy impossible. A perusal of the literature on the subject of "abnormal uterine bleeding" or "functional uterine bleeding" reveals that most articles consist of three parts, i.e., the reiteration of accepted facts, the brief recapitulation of the history of the subject, and a prolix discussion of the therapeutic values of the discussed agent. The second perusal of the literature discloses the alacrity with which many authors can get on and get off of the endocrinal bandwagon, with no evidence that they have profited by their enthusiastic errors of judgment. Inconsistency of interpretation of the clinicopathologic picture superimposed on an ever increasing trend to group all forms of menstrual aberrations as endocrinopathic manifestations is so prevalent as to confute even the established facts. Though disturbances of menstruation are symptoms of the variations in the ovarian-uterine relationship rather than entities, and it is the fashion of many to consider these variations as glandular in origin, nonglandular factors do play a major role and must not be overlooked. The widely used and abused term "functional bleeding" is limited to those cases in which, following a

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In Table I we have listed 1,500 cases, for which we have complete clinicopathologic data; no hormonal studies have been included. I have personally studied these cases. For convenience, we group our cases of bleeding into three major groups: (1) Those associated with the gestational states, (2) those with anatomic or functional diseases of the genital tract, and (3) those due to associated causes. In Fig. 1, the major causes are diagrammatically presented. In studies of this type it is difficult to determine the exact border between normal variations and actual pathology, but an honest attempt has been made to present, without bias, the purely clinicopathologic evidence. There is an overlapping of factors, for a large myoma must influence the ovarian and endometrial relationship; thus the possibility of coincidental occurrence must be considered. Most of these cases were treated as "functional

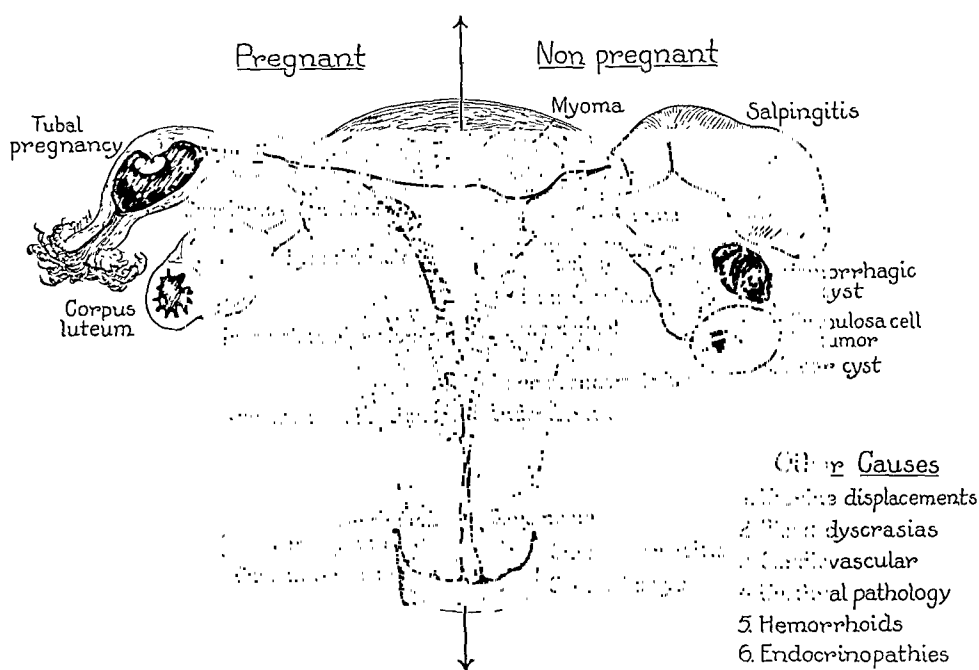


Fig. 1.

bleeding" prior to the final diagnosis, and the frequency of this misinterpretation will be emphasized in certain of the major classifications. For convenience of presentation, the series has been divided into two groups: first, those in which the actual specimen removed at surgery was studied or in which the diagnosis was made by visualization or palpation of the causative factors, and second, those cases in which the diagnosis was made with the assistance of endometrial and (or) cervical tissue examination.

CAUSE OF BLEEDING UNKNOWN

In 197 (13.1 per cent) instances, a careful study of the clinical history and removed corpus uteri offered no clue as to the cause of the patient's complaint of abnormal bleeding. In 84 of these cases we have sufficient ovarian tissue for histologic study and in all instances, evidence of

and frequently filled with dangerous consequences to the patient. The indiscriminate use of various advocated drugs, hormones, vitamins, and mechanical procedures is an indication of either the gullability of the clinician, the improper interpretation of the clinical findings, or actual ignorance. It is only proper at this point to add that I have been guilty of all three points on many occasions, therefore the casting of stones is performed by hands not entirely unstained.

The diagnosis of abnormal bleeding cannot always be made by any combination of history taking, physical examination, or the ordinary laboratory tests. A study of the endometrium is a valuable adjunct without which the diagnosis is often inaccurate and the resultant therapy empirical. Though hormonal studies are often helpful and even indicated in a few instances, the quantitative determinations reveal nothing of the qualitative activities of the hormones or the ability of the various organs to assimilate them. Bleeding may and does occur from any type of endometrium, and though the endometrial biopsy will indicate the type of endometrium, it does not always form a safe basis for the prediction of the cause of bleeding. Nor do the changes in the endometrial patterns permit a separation of primary or secondary ovarian involvement, thus the true value of the biopsy is its negative information.

TABLE I. MAJOR FACTORS INTERPRETED AS THE CAUSES OF ABNORMAL BLEEDING IN 1,500 WOMEN BETWEEN THE AGES OF 20 AND 40 YEARS, WITH THE PRIMARY COMPLAINT OF ABNORMAL UTERINE BLEEDING

Group A includes those cases in which either the specimen removed at surgery was obtained or the major factor was visualized or outlined by examination. Group B includes those cases in which the diagnosis was made with the aid of endometrial and/or cervical tissue.

THE MAJOR FACTORS	NUMBERS	PER CENT OF GROUP	PER CENT OF SERIES
<i>Group A:</i>			
Causes of bleeding unknown	197	27.0	13.1
Cervix, benign lesions	148	20.2	9.8
Myomata uteri	108	14.8	7.0
Ovary	76	10.4	5.0
Pelvic inflammatory disease	76	10.4	5.0
Cervix, malignant changes	57	7.8	3.8
Tubal gestation	27	3.7	1.8
Senile vaginitis	17	2.3	1.1
Endometriosis interna	16	2.2	1.1
Urethra	4	0.54	0.26
Rectum	3	0.4	0.2
Total	729		
<i>Group B:</i>			
Follicular phase	187	24.0	12.4
No changes; possible functional	124	16.0	8.2
Public	103	13.4	6.8
Endometrial polyp	102	13.2	6.8
Incomplete menstruation	82	10.6	5.4
Endometrial hypertrophy	70	9.1	4.6
Postabortal	53	6.9	3.5
Intermenstrual bleeding	33	4.3	2.2
General group	8	1.0	0.53
Postradiation	5	0.6	0.32
Tuberculosis	2	0.3	0.13
Abnormal gestation	2	0.3	0.13
Total	771		

reason for their use. Some clinicians have a routine schedule of injections, usually beginning with the estrogenic substances, then changing after a specified number of injections have been given. This is unfortunate, especially in large clinics, as the patient is frequently lost sight of and the injections continue over a period of years, the patient enjoying a probable psychic uplift from the injections and in time forgetting why she received the first treatment. The results of this varied form of therapy cannot be evaluated. Too frequently patients without demonstrable abnormalities return to normal, so far as bleeding is concerned, before the investigation is completed and proper therapy can be instituted. Thus, what constitutes proper therapy is questionable. A low hemoglobin can directly precede as well as follow menometrorrhagia, and it is extremely important to always bear in mind that the individual threshold of anemia, as a factor, varies considerably. A more complete preoperative study of the patients in this group and a knowledge of the limitations of various therapies along with an appreciation of the importance of constitutional disorders, may have prevented the indications for surgery in many instances.

THE CERVIX

In 148 (9.8 per cent) patients, the cervix was considered the source of the abnormal bleeding. Endometrial studies were made in 71 of these cases and 39 showed definite inflammatory reaction of the endometrium removed from the lower uterine cavity. This is consistent with our punch biopsy studies of the endometrium in the presence of chronic endocervicitis. The majority of these cases showed an actual extension of the inflammatory process into the lower portion of the uterus. That such an inflammatory process can serve as a causative factor is accepted, though frequently overlooked. In 91 cervices, polyps arising from various levels of the cervical canal were demonstrated. Bleeding in the presence of a polyp is usually metrorrhagic in type and varies markedly in amount. However, it is not uncommon to find even large polyps in the absence of menstrual aberrations. Apparently some other factor besides the actual presence of a foreign body may serve as the instigator to the abnormal bleeding in this group. Examination of the endometrium in the presence of cervical polyps has shed no light on the cause from this standpoint. The so-called "erosion" of the portio vaginalis of the cervix must also be considered, though the bleeding is usually very scant and tends to follow trauma.

The management of cervical lesions is threefold in type: (1) The interpretation of the pathologic changes by careful visualization of the cervix with properly taken biopsies, when doubtful areas are noted. We place little credence in either the iodine test or the colposcope, except for the psychologic effect which such procedures seem to have on the patient. Adequate exposure and good light seem sufficient. We feel that there is a tendency on the part of many to place too much dependence on the iodine test, and we have practically discarded it from our clinical armamentarium. To use the colposcope properly requires a thorough knowledge of the cervix, as visualized under magnification, a knowledge

normal cellular function is present. From a study of these cases post-operatively, it is our impression that hysterectomy in the presence of normal ovarian tissue is not followed by signs or symptoms of ovarian degeneration, though it does appear probable that some modification of the ovarian action may occur.

What is the microscopic appearance of normal ovarian function? Our interpretation is purely cellular and takes no notice of possible and even probable upsets of the ratio-relation between the various follicular responses and the effects such disruptions may have upon the uterus, the pituitary, and other glands of the body. There has been no constant relation between the presence of cystic ripening follicles and the endometrial patterns so far as the complete follicular cycle can be demonstrated. Normal appearing follicular elements with evidence of corpus luteum formation presupposing ovulation are accepted as the norm. But we do find normal appearing endometrium, myometrium, and ovaries in patients with clinical evidence of abnormal uterine bleeding. Selective staining of the vascular channels and the ratio of the myometrial elements has offered no clue to possible causative factors. Too many of the ovaries removed at the time of hysterectomy contain normal appearing corpora hemorrhagica, misinterpreted both clinically and pathologically as "chocolate cysts of Sampson." Ovaries with thin-walled cysts are removed and their importance as causative factors in abnormal bleeding is open to doubt, as many of them are nothing more than evidence of augmented ovarian activity. The endometrial pattern is correlated with the menstrual history, and though the fallacy of this is appreciated, the conclusions in this group are dependable from a clinical point of view. An attempt to link the presence of corpus luteum cysts as major factors in abnormal bleeding, especially when the endometrium is of the secretory type, is not conclusive. However, cysts of this type do apparently serve as a factor in some of the cases. To illustrate the discrepancy of endometrial response, we do find the follicular pattern as well as the luteal pattern in the endometrium associated with corpus luteum cysts. Thus another stumbling block to any theory of interrelationship is presented, and the value of the endometrial biopsy correlated with the pelvic findings is not absolute in its interpretation. Why these cases bleed and how to treat them are some of the bugbears of the investigative gynecologist. Fortunately most of the patients falling into this group, will, in spite of conservative therapy, recover spontaneously. It is highly probable that the glandular system can be disarranged temporarily, thus the admonition that so-called "functional" bleeding cases be treated conservatively as long as possible, hoping that the disrupted system will rearrange itself and a spontaneous recovery result. It is our opinion that many of the "cures" of the exploited agents frequently exposed as inert, would have recovered regardless of the medication employed.

One hundred and twenty-three of the 197 patients received endocrinal therapy in various forms, frequently supported with minerals and vitamins. A review of many of the therapeutic charts offers no logical

Myomas.—The relative infrequency of myomas as a possible cause of abnormal uterine bleeding is explained in our selection of the cases for this series. In the 108 (7 per cent) women with demonstrable myoma, the majority of the myomas were intramural in location. We have been impressed with the frequency of endometrial polyps occurring in the presence of myomas as a possible factor in the oft repeated statement that the endometrial pattern is of the endometrial hyperplasia type. A similar disorderly endometrial pattern is frequently present because of the pressure of the encroaching tumor on the endometrial layers. Dilated glands, dense stroma, and other changes consistent with the frequently accepted picture of endometrial hyperplasia lead to a misinterpretation of the causes of bleeding. This misinterpretation also accounts for the statistical studies showing an increase in the number of endometrial hyperplastic reactions as an indication of myoma-ovarian dysfunction factors in the origin of myoma. There is no demonstrable distinction in the symptomatology or in the pathologic picture of the myomatous and the nonmyomatous uterus. The subserous nodules have little effect on the uterine musculature while the nodule located in the submucosal position is often associated with diffuse hyperplasia of the uterine wall; a subsequent involvement is then frequently found in the neighboring endometrium. The intramural tumors are found with and without demonstrable hyperplasia of the surrounding tissue and the size of the tumor mass does not always predict the presence of these changes. Thirty-eight uteri showed no demonstrable changes in either the endometrium or the myometrium, except for the actual myomatous nodules, yet some of these cases with minimal tissue changes gave evidence of profuse and prolonged hemorrhage. Histologic studies of ovarian tissue in the presence of large myomas in 28 instances showed definite thickening of the tunica albuginea in 21 instances, sufficient to interfere with normal ovarian function. However, we do find large myomas in the absence of abnormal bleeding, showing normal endometrium and normal ovaries with corpora lutea. Thus, the presence of large tumor masses does not necessarily predicate abnormal ovaries. This mechanical impediment to normal ovarian activity may serve as one of the factors of abnormal bleeding; it may also be assumed on the basis of histologic study and the correlation of the clinical findings, that the menopausal symptoms, frequently the sequelae to hysterectomy for myomas, are not necessarily dependent on either the removal of the uterus or the mechanical interference of the ovarian blood supply. Our investigation does not support the frequent contention that endometrial hyperplasia, supposedly an indication of hyperestrinism, is a common occurrence in myomatous uteri. If our tissue studies have been correctly interpreted, there seems to be a definite ovarian dysfunction rather than a hyperfunction. It must be appreciated in this type of study that the presence of a myoma has classified the case as bleeding of an organic origin rather than of a possible so-called functional etiology.

Though not necessarily concerned with this study, careful examination of the round ligaments was carried out in every instance, and we

few of us have even without magnification. To acquire a working ability with this instrument predicates careful correlation between the visual pattern and the histologic findings in hundreds of cases. We feel that this instrument does have possibilities, but to advise its routine use by the practicing gynecologist, as a dependable adjunct in the ruling out of early malignant changes of the cervix, does not seem warranted. Our routine study of the cervix consists of adequately exposing the cervix, a strong light, careful cleaning of the cervix to remove foreign substance, palpation of the portio vaginalis preferably with the ungloved finger, and the excision of suspicious areas for microscopic study. (2) Adequate dilatation and study of the cervical canal to rule out polyps, canal abscesses and strictures, and endocervical malignancies. (3) Proper selection of either the cautery or one of the various surgical procedures.

The delicate application of the nasal tipped cautery to cervical gland cysts is only of cosmetic value, and when repeated at frequent intervals, may serve as a factor in producing strictures of the external os. If cauterization is indicated, it should be thorough. Local heat, either in the form of douches or by one of the many mechanical apparatus, is frequently of value before actual cautery or surgery, especially in the presence of marked infection and tissue edema. No cervical manipulation should be undertaken in the presence of an acute infection of the cervix or with demonstrable extension of the inflammatory process into the parametrial regions. We have stressed the importance of palpating the uterosacral ligaments, and the presence or absence of induration of these ligaments guides our therapeutic procedure. In this series, 4 women complained of severe lower abdominal pains following cauterization, and on examination were found to have either a flare-up of a previous pelvic inflammatory disease or an extension of the cervical inflammatory process into the parametria; 2 patients developed pelvic abscesses and 5 patients presented with abscesses of the cervical canal. Though not included in this series, we have post-mortem evidence of two patients who, following deep cauterization of acutely infected cervixes, developed streptococcal peritonitis and multiple abscesses scattered throughout the body.

Of the 91 polyps studied, malignant changes were demonstrated in one instance. A tissue review of 400 cervical polyps revealed 7 malignancies; this does not include those patients found to have fundal malignancies, associated with the incidental polyp. This is not a true index of the percentage of malignant polyps, as it is not an exaggeration to assume that approximately 25 per cent of the polyps removed are not subjected to microscopic study. A probable figure would be that 2 per cent of the polyps arising in the cervix will show malignant changes. The oft repeated statement that cervical polyps are found more frequently in women who have borne children is not consistent with our findings. Of 183 women with cervical polyps, 39 (21 per cent) women had never been pregnant; thus statistically speaking, polyps are nearly twice as frequent in women who have never borne children. In spite of the apparent low incidence of malignancy, every polyp should be subjected to microscopic study.

PELVIC INFLAMMATORY DISEASE

No attempt is made to separate the postabortal type of pelvic inflammatory lesion from the specific form. Of the 76 (5 per cent) cases presenting in this group, the bleeding probably results from disturbances to the ovary, sufficient to interfere with its regulation of menstruation. A second possible factor is the direct extension of the inflammatory process into the myometrium, thus preventing normal endometrial changes by disturbing the uterine vascular bed. The ovarian changes are usually mechanical, the capsule being thickened secondarily to the inflammatory process and thus preventing ovulation. It must be understood that the ovary does possess remarkable powers of rehabilitation, and all forms of conservative therapy should be utilized before resorting to surgery. As stated above, biopsy studies of the ovary at the time of pelvic surgery frequently permit prediction of the probable time of onset for menopausal symptoms. However, in many instances, leaving these grossly normal but physiologically impotent ovaries is of psychic rather than glandular importance. We have been unable to demonstrate any harm in leaving these physiologically inactive ovaries following surgery, and it does save both the surgeon and patient. The probability of such handicapped ovaries forming large cysts and thus requiring further surgical intervention is possible, and though this has long been an argument in favor of removing both ovaries, our studies do not support this argument. It is true that immediately following any type of pelvic surgery, one or both ovaries may become markedly enlarged. The majority of these enlarged ovaries will return to normal size in from two to three months without any form of therapy. The cause of this enlargement, even in the absence of actual trauma to the ovary or the tissue in its immediate vicinity, is not known. It is shown that hysterectomy following a previous bilateral salpingectomy is 8 times more frequent than oophorectomy following a previous hysterectomy and (or) salpingectomy. We have noted no evidence to support the statement that the removal of one ovary will alter the future activity of the remaining ovary, assuming of course that the remaining ovary is normal at the time of surgery. One of our patients whose right tube and ovary were removed along with the appendix at the age of 9 years, had three normal pregnancies and finally presented with a large symptomatic myoma. Biopsy studies of the remaining ovary showed normal functioning tissue. We have been impressed by the frequency with which the right tube and ovary are removed in the presence of appendiceal lesions, the operative diagnosis usually being cysts of the ovary or chronic inflammatory changes. Tissue studies usually reveal a low grade perisalpingitis. Both tube and ovary, if left intact, will return to normal within a very short period of time following the removal of the inflamed appendix. The use of the McBurney incision protects the left tube and ovary.

CARCINOMA OF THE CERVIX

Fifty-seven (3.8 per cent) women complained of irregular bleeding or spotting without either pain or the admitted knowledge of a pelvic

cannot ascribe to the statement that there is an associated hypertrophy of these ligaments in the presence of myomas. We do see definite enlargement of the round ligaments, but we also see definite atrophic changes.

THE OVARY

The most difficult group for classification are those cases in which the ovary is designated the precipitating factor, for even in the presence of large tumors, with a very small amount of demonstrable functioning ovarian tissue, normal function may be maintained. Frequently the bleeding may be the result of hyperemia secondary to the large pelvic mass. Histologic studies of grossly normal ovaries in the presence of symptomatic retroposition of the uterus, myomas, or chronic inflammatory lesions of the pelvis will often disclose a definite increase in the fibrous tissue with an associated decrease in the epithelial elements of the ovary. That such an increase of inactive elements in the ovary predicates a decrease in the normal function of the gland is a logical deduction. However, what degree of upset in the fibrous-epithelial tissue ratio determines a derangement of function must vary with the individual; here again enters that so-called refractive index of ovarian-uterine relationship. This inability to determine the passing of the ovarian tissue pattern from the normal state to that of a pathologic state adds to the difficulty of indexing the ovary as a factor in the cause of abnormal uterine bleeding. However, abnormal changes in the ovaries of 76 patients (5 per cent) were accredited as being the cause of this disorder. In reviewing more closely the clinical manifestations of this group, we could find no typical bleeding pattern peculiar to ovarian pathology. There were 7 malignancies of the ovary, and of these, 5 had received various forms of endocrine therapy. Granulosa cell tumors were present in two instances and one of these patients had received large amounts of estrogenic substance over a period of five months prior to surgery. Hemorrhagic cysts and other types of cysts arising from the follicular apparatus accounted for the remainder. The absence of dermoid cysts, fibroma, and endometrial cysts is explained by the fact that they are usually associated with pain as the outstanding complaint.

Regardless of the increasingly voluminous reports on the importance of the uterus in relation to normal ovarian function, we feel that if the tissue study of the ovary at the time of hysterectomy reveals normal functioning follicular elements, the function will continue as normal after the removal of the uterus. We base this conclusion on the clinical findings of these patients following surgery. It must be admitted that the proper procedure would be to re-examine the ovaries several years following the first examination, but this is a difficult thing to do. We do not think that experimental studies in lower animals can be transposed to include women, so far as this reaction is concerned. By carefully studying the ovaries it is possible to predict whether or not the patient will develop menopausal symptoms following surgery. It must be stressed that what constitutes clinical evidence of ovarian dysfunction is not too dependable from a statistical approach.

ENDOMETRIOSIS INTERNA

Heterotopic endometrial tissue was found in the myometrium of 16 (1.1 per cent) uteri, removed with the diagnosis of "fibrosis uteri" and because of uncontrollable uterine bleeding. Though this lesion is not a rare entity, menstrual distress rather than abnormal bleeding is the predominant complaint. Adenomyomas were also a frequent occurrence in the myoma group. Bleeding is probably due to a lessened efficiency of uterine musculature, and also secondary to a congestion of the endometrial venous plexus, arising from the interference to the normal vascular bed.

THE URETHRA

Adequate proof that the patient's interpretation of her complaint is of little factual value is well borne out by 4 (0.26 per cent) patients complaining of abnormal bleeding; examination in each instance revealed the urethra as the source of the bleeding.

THE RECTUM

This group should be classed as an oddity. Three (0.2 per cent) patients with suspected uterine bleeding were found to have bleeding hemorrhoids. Of further interest is the history of one patient who had been treated extensively with endocrines; little relief was obtained with this form of conservative therapy.

CASES INTERPRETED WITH THE AID OF ENDOMETRIAL STUDIES

The Follicular Phase.—In 187 (12.4 per cent) patients, a thorough general and pelvic examination revealed no cause for the abnormal bleeding. In the majority of these cases the basal metabolic rate was also studied. Endometrial studies showed histologic patterns, consistent with those changes interpreted as occurring in the follicular or proliferative phase of the menstrual cycle. It is well understood that single punch specimens removed from the fundal portion of the uterine cavity do not always give the true endometrial picture, but this site is the most dependable and consistent in its response. Unfortunately it is in this group that our data do not permit an exact corroboration of the cyclic endometrial changes with the calendar phase of the menstrual cycle. To obtain such data, it is necessary to have dependable records of consecutive menstrual periods, tabulated by the patient at the time of occurrence and not by memory during her visit to the clinic. Hospital records and dispensary notes are of no value. Of the 187 studies, there are 8 endometria interpreted as typical endometrial hyperplasia. It is difficult to determine whether the condition commonly termed endometrial hyperplasia is the same as the one to which Cullen first applied the term, or whether the endometrial changes often discussed are due to hypertrophy, to edema, to which the term endometrial hyperplasia has been loosely applied. This common discrepancy and loose handling of terminology is a serious obstacle to statistical studies. In favor of these 8 cases being true hyperplasia, secondary to hyperestrinism, is the fact that regardless of the various forms of hormonal therapy and repeated

mass. No early (Stage I) cases were found, and the youngest patient was 23 years of age; this patient received hormonal therapy for a period of eleven months prior to her first pelvic examination and finally came to the clinic because she was not satisfied with the type of treatment she was receiving. Twenty-three patients in this series received various forms of hormonal therapy; only 19 of the 57 patients gave a history of having had a pelvic examination before admission to the clinic. Of the 57 patients, studies of the endometrium were carried out in 41 cases, and of this group 2 showed changes suggesting endometrial hyperplasia. Subsequent biopsy studies of the endometrium were impossible because of the early institution of therapy. In two instances carcinoma of the fundus was found on curettage. One with the malignancy limited to an endometrial polyp revealed no further malignancy of the endometrium following hysterectomy. This is not a rare incident, though very disquieting to the pathologist who has not been too certain of the primary interpretation of the tissue removed by curettage. The relative paucity of fundal malignancies in this series is explained on the age limitations.

TUBAL GESTATION

Though the diagnosis of ectopic pregnancy, following the rupture with intraperitoneal hemorrhage, is not difficult, the so-called silent tubal pregnancy offers diagnostic problems. In 27 (1.8 per cent) cases, tubal pregnancy was erroneously diagnosed prior to surgery. The complaint was bleeding, and the most frequent diagnosis was pelvic inflammatory disease. In none of these 27 cases was pregnancy suspected. The value of the endometrial biopsy, in the presence of uterine bleeding as a diagnostic adjunct, is dependable if the tissue shows definite decidual changes in the endometrium. That decidualike changes in the endometrium can occur in the absence of pregnancy has been proved, and though the finding of a decidualike reaction is suggestive, the study of the endometrium in this group was of little value.

SENILE VAGINITIS

Of the 17 (1.1 per cent) women with senile vaginitis, 9 had received radium for "benign functional uterine bleeding"; subsequent investigation showed that none had endometrial studies prior to irradiation. Five of the 9 radiated patients received their treatments before the age of 25 years. Three patients had been radiated for "temporary sterility," with subsequent permanent destruction of the ovarian activity, followed by atrophic changes of the vaginal mucosa. The response of this type of vaginitis, to specific hormonal therapy, has been very disheartening in our hands. Pelvic "house cleaning" for extensive endometriosis accounted for the remaining 5 patients. A review of the pathology of one of these cases revealed that the "chocolate cysts of the ovaries" were simple hemorrhagic cysts with ample normal ovarian tissue to warrant excision of the cysts rather than radical extirpation. Patients with infectious or chemical vaginitides complain of discomfort rather than vaginal spotting.

frequently only temporary. Studies made on the ovaries of individuals who have received various forms of gonadotropic substance frequently reveal tissue totally impossible of stimulation. Since, however, most patients give a history of having been benefited by the injections, the influence is either on a psychic basis or the injected substance must act directly upon the uterus.

NO CHANGES; POSSIBLE ENDOCRINOPATHIC MANIFESTATIONS

The clinical histories are accurate enough in 124 (8.2 per cent) instances to permit a factual correlation of the endometrial pattern with the patient's menstrual history. The usual complaint is of several profuse periods, following a preceding normal menstrual history. Not infrequently a careful questioning will reveal that the patient has had similar episodes of abnormal bleeding over a period of the past few years. The most satisfactory therapy is symptomatic treatment of the occasional associated low grade anemia. However, low grade anemia is so common among the female patients of a large charity clinic, that its importance as a factor in this group must be open to doubt. The majority of these patients will return to a normal cyclic menstrual life with or without the benefit of any type of treatment. In most of these cases, the endometrial studies have offered no clue as to why the patients are bleeding and the majority of the endometrial patterns are of the luteal type, suggesting normal ovarian activity. Then there is the patient with the definite anemia, complaining of symptoms suggesting general debility, who occasionally gives a history of profuse bleeding, but more frequently complains of periods of amenorrhea.

THE PUBLIC

For want of a better descriptive term, we have used "The Public," to include those 103 (6.8 per cent) patients who, after careful questioning and examination, including endometrial studies, were assured that their menstrual periods were normal. It is this type of patient, susceptible to advice from the medical columns, the advertising brochures, friends, and family, that must be handled with the utmost care. Gathering pathologic evidence supports our impression that the continuous injudicious use of substitutional hormonal therapy, in the presence of normal functioning glands, will produce permanent destructive changes in the ovary. Relying solely upon the patient's unsupported statement that her periods are abnormal predicates, in many instances, improper and possibly dangerous therapy. The correct handling of this group necessitates a careful explanation to the patient that normal periods vary in cyclic appearance, duration of flow, and amount of blood loss. Simple placebos may be of value in some instances.

ENDOMETRIAL POLYP

The curettings from 102 (6.8 per cent) patients were interpreted as being endometrial polyps; certainly they are more common than usually accepted. The abnormal tissue response with the "Swiss-cheese" pattern leads many an unversed pathologist to diagnose endometrial hyperplasia.

curettage, hysterectomy was finally resorted to in order to control the uterine hemorrhages. The term endometrial hyperplasia has been bandied about with little attempt to apply it properly. In the first place it is a poor descriptive term, for a careful detailed study of the stroma will reveal that there is not an actual hyperplasia of the cellular elements, the increased density being the result of the increased size of the endometrial glands. Second, its persistent misuse in practically all benign derangements of the endometrial patterns has rendered it of little scientific value. Careful review of the many articles and their attended photomicrographs and case reports supposedly of endometrial hyperplasia, amplify the fact that the majority of the cases are not endometrial hyperplasia. Endometrial hyperplasia is that change in the tissue pattern associated with a marked and persistent overproduction of the estrogenic substance, a total absence of ovulation, and a clinical history of profuse uterine hemorrhages interspersed with periods of amenorrhea. The changes associated with persistent failure of ovulation, either the result of mechanical or physiologic impediments to normal ovarian activity, are not endometrial hyperplasia. The entire interpretation is so muddled and poorly understood that a dogmatic classification is impossible, as well as impractical. This ovarian dysfunction, associated with interference of ovulation, causes changes corresponding to the middle follicular or proliferative phase of the menstrual cycle; to apply the term endometrial hyperplasia to all endometria, because of variations in the size of the glands and possible alterations in the density of the stroma, is not consistent with the clinicopathologic investigations. This tendency to misinterpret the histologic picture has brought about confusion in the literature, because many of the therapeutic claims are based on these wrong interpretations.

Monthly endometrial biopsies from accepted normal women over a period of several years reveal that anovulatory periodic bleeding does occur in the absence of either demonstrable anatomical, endocrinal, or constitutional abnormalities. Thus the presence of the follicular type reaction of the endometrium in the late luteal phase of the menstrual cycle does not necessarily indicate either abnormal ovarian action, pathologic changes in the uterus, or permanent upset in the polyglandular relationship. A single biopsy specimen, though valuable, must be interpreted with each case; carefully tabulated menstrual calendars supported by comments on the emotional, constitutional, and physical upsets are a necessary adjunct to correct interpretation of the ovarian-uterine relationship. Thickening of the capsule of the ovary, preventing ovulation, with subsequent corpus luteum formation, in most instances is followed by a persistence, but not an oversecretion, of the follicular substance. Thus the endometrial picture is one suggesting a prolonged but rather sluggish response, instead of a hypersecretion of the estrogenic substance associated with endometrial hyperplasia. The importance of the anterior lobe of the pituitary gland in these cases is appreciated but still speculative. Though gonadotropic therapy will elicit an occasional response suggesting reactivation of the ovaries, the response is all too

time. We have grouped these various changes with their numerous in-explainable ramifications as endometrial dysplasias, which applies only to an abnormality of form, without implying either the cause or the type of the abnormal changes.

POSTABORTAL

Though the patients in this group strongly denied the possibility of pregnancy, both before and following the curettage, 53 (3.5 per cent) patients had endometrial changes consistent with retained secundines, evidence of previous intrauterine pregnancy. Into this group should be placed some of the so-called "follicular type" of endometrii, for the diagnosis of retained secundines is not always possible after the patient has bled for several days. One is impressed by the frequency with which conception apparently can occur in human beings without the benefit of the male factor. It is of interest that many of these patients had received hormonal therapy; this type of patient rarely gives an honest answer to the physician's questions, and therapy frequently varies so much as to be ludicrous.

INTERMENSTRUAL BLEEDING

Thirty-three (2.2 per cent) women stated that they bled at regular two-week intervals, and as a rule, one period was several times longer than the other period. Eighteen of these patients were married and none of them had ever been pregnant. Explanation to the patient of a probable cause of the sterile marriage was followed by pregnancies in 7 cases. Most of the intermenstrual periods were associated with a sense of discomfort, the discomfort varying conversely with the amount of blood flow. Twenty-one of the patients had undergone surgical procedures; 18 for the removal of the appendix, and three for operations of the ovary. In no instance did the surgical procedure bring relief for the discomfort complained of by the patient prior to the operation. Twenty-six of these patients had received hormonal therapy for this accepted physiologic phenomenon. Why these patients bleed is another unanswered problem in our study of the menstrual phenomenon. Suffice to add that we know of no form of effective therapy.

THE GENERAL GROUP

Into this group we have placed 8 (0.53 per cent) patients, including one with acute lymphoid leucemia whose subsequent postmortem studies revealed almost a solid infiltration of the ovaries and uterus with round cells; I wrongly interpreted the endometrial biopsy as an acute endometritis. Four of the cases were proved cardiac problems, 3 having been treated for the uterine bleeding, with no attention being given the evidence of gross cardiovascular pathology. The menstrual periods became normal in every instance following proper treatment of the cardiac failure. Unfortunately, our experience is limited with this group, as the medical clinics appreciate the relationship of such conditions to abnormal bleeding and treat the bleeding as a minor symptom of the general picture.

We have also been impressed with the frequency of endometrial polyps in the absence of abnormal bleeding. Here again, other factors than the presence of a foreign body in the uterine cavity must be looked for to account for the bleeding. A thorough study of the removed tissue, with an appreciation of the microscopic changes consistent with the polyp, will clarify the diagnosis. The missed diagnosis of the polyp accounts for the excellent therapeutic results of those cases interpreted as endocrinopathic manifestations.

INCOMPLETE MENSTRUATION

Though this is a relatively new addition to our interpretation of endometrial patterns, we have listed 82 (5.4 per cent) cases in this group. We are uncertain in some instances as to whether or not we are dealing with small polyps or an incomplete menstruation. The actual interpretation of the tissue changes is still unsettled, and we recall listing some of these cases as "peculiar foreign body-like reactions." It is also possible that a small fragment of retained endometrium, with its subsequent interference to normal tissue response, may later develop into a true endometrial polyp. Serial sections of uteri offer support to this possibility, but have not as yet given us sufficient evidence to advance it as a proved fact.

ENDOMETRIAL HYPERTROPHY

Seventy (4.6 per cent) patients were diagnosed as having either a malposition of the uterus, partial descensus of the uterus, or pelvic varicosities, on the basis of changes in the endometrial patterns. An occasional patient with symptomatic uterine malposition, complaining of profuse and prolonged periods, will experience relief from the menstrual aberration following mechanical correction of the malposition. The endometrium, which prior to the correction contained an increased number of blood vessels, and also showed an increase in the number of glands for the calendar date of the menstrual cycle with a definite increase in the density of the stromal cells, will return to an accepted normal pattern within several months following correction. However, if the mechanical interference has been present long enough to bring about permanent changes in the myometrium, the correction of the interference will have no effect on the menstrual aberration. This fact must be appreciated when surgical intervention for correction of the malposition of the uterus is contemplated and also accounts for the all too frequent failure of the surgical procedure. Thus, the so-called hypertrophy is secondary to the hyperemia of the uterus induced by mechanical changes in the vascular bed of both the pelvis and the uterus. The personal factor must also be accepted, as many cases with sufficient demonstrable changes in the pelvic supports to warrant extensive interference with the vascular bed, present no abnormalities whatsoever. With the rapid progress in our knowledge of the endometrial changes, the descriptive terminology should be revamped. However, our knowledge is far from complete, and it is better that we struggle along with the present inapt system than to apply improper terms at the improper

spite of anatomic lesions, other factors must be considered as probable etiologic causes precipitating the abnormal bleeding. We are of the opinion that the surface of this subject is just being scratched, and that not only must the problem be approached from an endocrine angle, but the clinicopathologic aspects must not be forgotten or discarded because of the waves of therapeutic and investigative enthusiasm.

SUMMARY

1. A series of 1,500 women between the ages of 20 and 40 years, complaining primarily of abnormal uterine bleeding, are presented from a clinicopathologic approach.

2. The misinterpretation of the endometrial patterns and the misapplication of terminology have done much to complicate the present status of investigative and therapeutic work in menstrual aberrations.

3. Though endocrinopathic manifestations are important factors in the cause of abnormal uterine bleeding, factors of anatomic nature are more common and should be ruled out before interpreting the cause as functional or dysfunctional in type.

4. Therapy, to be adequate, demands a thorough and complete investigation of the entire system with a proper interpretation and appreciation of the findings.

5. No attempt has been made to offer new theories, change the classification, or advance new ideas of therapy; the clinical aspects of the case and the associated tissue changes have been studied and presented with personal interpretations.

523 WEST SIXTH STREET

THE ROLE OF THE FALLOPIAN TUBES IN THE SPREAD OF PELVIC CANCER

REPORT OF A CASE WITH A BRIEF REVIEW OF THE LITERATURE

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THE question of the transtubal cancer dissemination is of high clinical significance as well as of pathologic interest and has been given a great deal of attention by numerous investigators. In reviewing the literature on this problem, Reichel,¹¹ in the year 1888 was probably the first to draw attention to the Fallopian tubes as a possible passageway through which cancer cells may travel. He reported two cases of ovarian carcinoma, each associated with a small carcinoma of the uterine mucosa. In his discussion of the presumable origin of the uterine growths in these two cases, he suggested the new idea that they may have arisen from the implantation of cancer cells escaping from the ovarian carcinoma through the lumina of the tubes.

The importance of this subject was at once apparent to the gynecologist and surgeon.

V. Franqué² was the next to describe an instance of primary sarcoma of the uterus in which particles of the uterine growth microscopically were found to be

POSTRADIATION

Though squamous cell metaplasia of the endometrium is no rarity, its presence is frequently very confusing to both the pathologist and the clinician. Five (0.32 per cent) patients gave a history of radiative castration for benign uterine hemorrhage, and subsequent study of the endometrial changes showed definite benign metaplastic changes. This cellular change is probably the end result of a persistent chronic irritation, but an additional factor must be included to account for its not being a more frequent change in the rapidly increasing number of cases receiving this type of uncontrolled therapy. The routine use of small dosages of x-ray or radium to control bleeding and effect a "temporary amenorrhea" in young women is injudicious because of the wide variability in the individual responses to irradiation. There is also increasing evidence adding more probable hazards to irradiation. It has been definitely shown that defective embryos may be produced after irradiation and may also influence the subsequent generation. Though this evidence has been limited to lower forms of life, it warrants serious consideration before advising routine irradiation in young women. The bleeding in these cases is usually scant, and described as a profuse, foul, blood-streaked discharge. We always suspect malignancy and usually find a partial to complete atresia of the cervical canal. True pyometria has not been included, as this type of case presents with pain and discomfort.

TUBERCULOSIS

Though we have access to a large tubercular clinic, only two instances of endometrial tuberculosis are included in our series. In each instance the preoperative diagnosis was wrong.

ABNORMAL GESTATION

To our incomplete abortions and our ectopic pregnancies, we must add one hydatidiform mole and one chorionepithelioma. The mole was correctly diagnosed by the nurse on duty prior to examination by the attending physician. The chorionepithelioma was apparently limited to the uterus and was also diagnosed correctly preoperatively. Lutein cysts of the ovary were present in both cases and returned to a palpable normal size within a period of three months following surgery.

DISCUSSION

A lengthy discussion is not indicated in this report. We have made no attempt to summarize even the most recent work in this field. We have merely outlined our findings and our interpretations as we have seen them. Our interpretations and our deductions are necessarily influenced by the works of Bartelmez, Cullen, Corner, R. T. Frank, Fluhmann, Hamblen, Hartman, Haigs, Novak, and many others. A brief summary of the group reveals no typical set of symptoms peculiar to specific pathologic changes of either the uterus or the ovaries. The patient with the minimum of demonstrable changes may bleed more profusely than the individual with widespread pathologic changes in the pelvis. Running through the entire picture is the apparent fact that, in

ligation of the fimbriated ends of both Fallopian tubes, great care and gentleness in pelvic examination, and warned of the use of radium as well as of the abuse in employing diagnostic curettages.

In a later paper, Sampson¹⁵ modified some of those rules, particularly his reaction toward the use of radium, and now recognizes the therapeutic value of the proper intrauterine radium application in carefully selected cases of carcinoma of the body of the uterus, in spite of some dangerous disadvantages occasionally occurring from its employment.

Norris and Vogt⁷ reported the results of a study of 115 cases of carcinoma of the body of the uterus. Metastases were observed only in two instances in the ovaries and once in the tube; the great majority of the secondary growths were found in the pelvis. The authors are advocates of Sampson's endometriosis implantation theories and believe it is at least possible that a similar condition may occur in the case of carcinoma cells originating within the uterine cavity.

Sampson's conception of the significance of the Fallopian tubes as a noteworthy pathway for the dissemination of malignant tumors of the uterine mucosa was bound to cause much concern among the orthodox believers in the lymphatic route, and his findings and views were subjected to revision by subsequent authors.

Novak^{8, 9} was among the first and strongest opponents. A critical analysis of Sampson's paper of 1924 as well as his own investigations led him to the opinion that Sampson has attributed too much importance to the occasional findings of free cancer particles in the lumen of the Fallopian tube. He expressed the belief that the description of those several cases upon which Sampson's views were mainly based presented no definite evidences for considering that these broken off particles are also responsible for the further spread of the cancer. In discussing the various routes by which the growths might have extended, he emphasized that they had been disseminated through the usual lymphatic channels: "certainly this route cannot be excluded, and, as this is the recognized route for cancer dissemination, it cannot be disseminated without much stronger evidence than is contained in Sampson's paper."

Robinson,¹² in a study on primary and secondary ovarian tumors, accepts only the lymph and vessel routes through which metastases may take place. He pointed out that the cancer tissue in secondary ovarian, tubal, and uterine carcinoma is located within the lymph spaces or blood vessels of the stroma, and that the lining epithelium of these organs presents a normal appearance. It was found that secondary ovarian carcinoma is characterized by the absence of any epithelial involvement, so that the differentiation between primary and secondary carcinoma of the generative organs, at least in the earlier stages, should not present a problem. Robinson believes that the contemporaneous appearance of malignant papillary tumors, within ovarian cysts and upon the surface of the ovaries, and similar growths of the uterine and tubal mucosa as well as the serosa covering these organs, "is due to the same biologic factors influencing variously located and metamorphosed epithelial centers of a common genetic source."

Offut¹⁰ discussed the subject of the relationship of carcinoma of the body of the uterus and of the ovaries. The histories of 520 cases of adenocarcinoma of the body of the uterus and 616 cases of papillary cystadenocarcinoma of the ovaries in which operation had been performed in the Mayo Clinic from 1913 to 1930 were reviewed. In 11.9 per cent of the cases of carcinoma of the body of the uterus and in 8.6 per cent of the ovarian growths there was carcinoma in both organs. The specimens from 53 of these cases were chosen for intensive microscopic study which revealed 5 cases of primary uterine carcinoma with metastases to the ovary, 16 cases in which the lesion was found to be primary in the ovary and secondary in the uterus, 31 cases in which the situation of the primary lesion could not be determined and 1 case with apparently independent carcinoma in both organs. In 15 of these 53 cases, secondary involvement of the tube was present, and in "several" instances cancer cells were noted in the lumen of which lymph- and blood vessels were normal. In an attempt to determine the various possible modes of extension by which carcinoma might have spread in these cases from the uterus to the ovary and vice versa, Offut expressed the opinion that the Fallopian tube should be regarded as one of the routes through which cancer may be disseminated.

lying free in the lumen of the right tube. Metastases of sarcoma were present on the surface of the right ovary, in the right broad ligament, and in the anterior vaginal wall. From the description given, it seems evident that the tubes have undergone inflammatory changes. The 53-year-old patient had a preliminary curettage two weeks before she was operated upon. Franqué was inclined to regard the transportation of tumor particles from the patent fimbriated end of the Fallopian tube into its free lumen in this case as probable but not definitely proved.

Morinaga⁵ reported a second case from v. Franqué's clinic and his description of a primary carcinoma of both the Fallopian tubes with secondary uterine growth is rather remarkable in its completeness and observation.

Glendining³ described two cases of stomach carcinoma with secondary ovarian growth. In both observations cancer cells were present in the lumina of the Fallopian tubes as well as in the mucosal lymphatics. In discussing the origin of this interesting pathology Glendining assumed that cancer cells entering the lumina of the Fallopian tubes by their fimbriated extremities, became implanted in the tubal mucosa and from thence invaded the subepithelial lymphatics and the lymph vessels of the mesosalpinx. He finally concluded that the possibility of the origin of the tubal carcinoma from the ovarian growths by way of the lymphatics cannot be entirely excluded.

Sitzenfrey¹⁸ reported an instance of carcinoma of the uterus associated with the presence of free bits of the uterine growth in the lumen of one of the Fallopian tubes. No evidence of carcinoma invading the tubal mucosa itself could be demonstrated in the Fallopian tube.

Schiller¹⁷ added another observation of free cancer particles in the tubes of a specimen of primary carcinoma of the body of the uterus. The case presented many points of interest. The uterus contained an extensive advanced adenocarcinoma of the glandular type and the clumps of cancer cells lying free in the right tube showed the same histologic structure as the large uterine tumor. In some places both tubes exhibited the features of chronic salpingitis with marked chronic inflammatory changes of their walls. Carcinoma was not found to be present in the lymph channels in any portion of the specimen. It is interesting to note that the external uterine os was occluded. The patient was 49 years of age and the last menstrual period occurred six months before the operation. Schiller agrees with the opinion given by Sitzenfrey that secondary tubal carcinoma may arise from this source and that with a further migration of these particles implantation of this growth on the surface of the ovary and peritoneum may develop. This displacement of the tumor fragments into the tube may be explained by assuming that these particles were pressed into the tube by contractions of the uterus, and on the other hand, that the normal peristalsis of the tube and the action of its ciliated epithelium were not strong enough to resist this retrograde invasion.

In recent years disagreement as to the importance of the transtubal cancer dissemination has arisen in the American literature, while in the British and German literature less attention has been devoted to this problem. The question as to whether or not the transtubal migration of cancer cells plays a role in the spread of pelvic carcinoma has become a matter of controversy and it may be of interest to review briefly the most significant opinions.

Sampson,¹³⁻¹⁶ in 1924, presented a fundamental study, dealing with the pathologic conditions arising from the implantation of tissue and epithelium which escapes through or from the Fallopian tubes into the peritoneal cavity. He had also shown that particles of malignant endometrial tumors, at times, escape into the lumina of the tubes or may be forced into as well as through them by manipulations of the uterus such as ungentle pelvic examination, curettage, and other surgical procedures. Convincing evidence was shown indicating that implantation of these fragments sometimes occurred in tubal mucosa, and on the surfaces of the ovaries and peritoneum. On the basis of these new findings and of his previous investigations, Sampson laid down several rules in the treatment of cancer of the body of the uterus to prevent its transtubal dissemination. He advised abdominal hysterectomy starting with the

Operation.—Under lumbar anesthesia a long median incision was made from the symphysis, extending about 2 inches above the umbilicus and encircling the latter. After opening the peritoneum, the umbilical nodular mass was excised with the overlying skin. The peritoneal cavity contained a small quantity of serosanguineous fluid. The serous surface of several coils of bowel was covered with minute nodules and plaquelike elevations. These lesions were round or oval in shape and only slightly raised above the surface. They varied in size from a pin's head to several millimeters in diameter. The color was ochre yellow, but varied here and there from light yellow to light brown. The smallest tissue islets were very soft, and the larger, apparently older ones were of a firmer, somewhat rubbery consistency. A few similar elevations were also seen on the surface of the fundus of the uterus. The bottom of Douglas' pouch was filled with some loose, friable, and yellowish tumor material which was easily removed by hand. The peritoneal surface of Douglas' pouch itself, however, showed a smooth, glistening, and intact serous covering. No palpable or macroscopically visible metastatic nodules were observed in the liver or stomach, and the omentum appeared to be normal. There were some adhesions around both adnexa, especially around the region of the left ovary. The latter was found to be enlarged to nearly twice the normal size. The enlargement was due to a mass, very friable and soft in consistency and of greenish-yellow color. The ovarian tumor closely resembled a large cystic corpus luteum, but later proved to be a solid mass. The entire uterus and both adnexa were removed in the usual manner. There was some difficulty in enucleating the ovarian tumor from its dense adhesions because of the extreme friability of its tissue. The nodule in the posterior cul-de-sac was found to be well circumscribed and of superficial character. There was no apparent connection with the cervix. Metastases to the retroperitoneal lymph nodes were not detected. Drainage of the paravaginal space was made by passing a strip of iodoform gauze into the vagina. The pelvic peritoneum and the sigmoid were united over the gauze strip, burying the stumps and causing complete peritonization. The omentum was brought down and the incision closed in layers.

The patient made an uneventful recovery, left the hospital twenty-two days after operation, and was referred for deep x-ray therapy. She reported at stated intervals, and her condition remained perfectly normal except for some moderate vasomotor disturbances which were treated endocrinologically. Nine months after the operation the patient had gained about twenty-five pounds. Pelvic examination made four years after operation was normal, there being no evidence of any recurrence of the carcinoma.

Pathology.—*Gross examination:* The specimen removed at operation included the uterus to which both tubes and ovaries were attached. In addition, there were two separate nodular masses about 3 and 4 cm. in diameter. The uterus was 7 cm. long, 4 cm. broad in its greatest transverse diameter, and 3.5 cm. in its antero-posterior diameter. Except for the above described tissue islets and some adhesions clinging to its surface, the perimetrium was smooth and glistening. The uterus was soft in consistency and the cavity was almost completely filled with a polypoid tumor mass arising from the anterior wall of the fundus. It was yellowish in color, very soft, and friable, and as big as an olive. The growth pointed downward, projected through the internal os and covered the endometrium. The mucosa lining the uterine cavity apparently had been replaced by a superficial carcinoma, presenting a whitish gray translucent color. The uterine wall averaged 1.5 cm. in thickness. The cervical canal was rather short, but the mucosa was apparently unchanged. The left ovary was transformed into a solid tumor mass 6 by 4 by 4 cm. and covered by numerous adhesions. The surfaces made by cutting showed it to be made up of a yellow, soft, friable mass, which appeared to contain fatlike substances not resembling ovarian tissue. The right ovary and Fallopian tube grossly appeared normal. The left Fallopian tube was 7 cm. long and covered by a few adhesions; its outer third was slightly dilated. The nodule excised with the umbilicus contained a cavity 2 cm. across and was filled with yellow reddish necrotic material. The tumor mass removed from the posterior cul-de-sac was solid and grossly appeared to be malignant.

Microscopic examination: The whole corporeal mucous membrane was found to be converted into an extensive papillary adenocarcinoma extending downward into

The following case is reported in some detail because a careful search of the literature has failed to reveal any case with a similar combination of pathologic findings, justifying the assumption of transtubal cancer dissemination.

CASE REPORT

A white female, 43 years of age, was admitted to the hospital, complaining of fullness and heaviness in the lower abdomen, shortness of breath, and of a painful swelling of the umbilicus.

The family history was essentially negative. Her father died of ileus; her mother died of myocarditis.

The patient had measles and chicken pox in childhood. At the age of 13, she is said to have been treated for "apex pulmonary catarrh," and thirteen years later she developed a tuberculous tendovaginitis of the right hand.

Menstruation had begun at 13 years of age, and for three years had been regular, lasting from two to three days, and was moderate in amount. At times there was pain in the back and in the ovarian regions. At 16 years of age she did not menstruate for three months, and then the periods had changed in amount and duration. They lasted only one to two days and were very scanty. The menstrual history showed that she passed an apparently normal menopause one year before admission, at the age of 42. There was no discharge except at menstrual periods.

She denied venereal infection, was unmarried, and never had been pregnant. Patient drank no alcohol and used no tobacco.

Her present illness dated back for about two years, when she had noticed a slowly enlarging swelling of the abdomen associated with some shortness of breath on exertion. She was fairly well until two weeks before admission when she first noted a small lump in her navel which grew larger, became distinctly painful, and had never retrogressed. She could recall no history of injury to the part but thought injury was probable. There was no discharge from the navel. Except for an increasing dyspnea there were no other subjective complaints.

On admission, general examination revealed a well-developed, fairly well-nourished female. The temperature, pulse, and respiration were normal, and the systolic blood pressure was 130 mm. Examination of heart and lungs was negative. The abdomen was found symmetrically distended and bulging due to the presence of a great deal of free fluid. The skin over the umbilicus was of a distinct dark, bluish discoloration, and slightly edematous, but freely movable over a more deeply situated, rather firm, nodular mass, about the size of a walnut. The mass was buried in the fatty tissues of this region, attached to the deeper structures and not well outlined. Serologic tests for syphilis, as well as urine and stools were negative; sedimentation rate and blood chemistry were normal.

Eight liters of clear, yellowish fluid were removed by paracentesis showing a specific gravity of 1.025 and alkaline reaction. The sediment contained an abundance of lipid droplets. Following paracentesis, no masses could be felt abdominally, aside from the nodular swelling in the region of the umbilicus. The liver and the spleen could not be palpated. Roentgen ray examination of the chest and stomach revealed no changes. On rectoscopic examination, the mucosa was normal.

Gynecologic examination revealed normal external genitals; the hymen was intact, but permitted introduction of the examining finger and of a virgin speculum. Both lips of the portio were extensively eroded. The body of the uterus was normal in size, symmetry, anteflexed, firm in consistency, and movable. In the left adnexal region an indefinite mass was felt which could not be definitely made out because of some muscular rigidity and tenderness. No pathology was palpable in the region of the right adnexa. Some tenderness was obtained in the cul-de-sac of Douglas on firm pressure. A distinct, well-circumscribed, firm tumor mass about the size of a plum was felt in the cul-de-sac on combined vaginal and rectal examination. On the basis of the above clinical history and physical examination, a tentative preoperative diagnosis of ovarian carcinoma with peritoneal implantation was made. Surgical intervention was therefore recommended.

In some places the epithelial cells formed small cystic cavities having little treelike papillary excrescences extending into their lumina while in others the proliferating glandular epithelium tended more to the formation of small solid cell nests. The gland cavities, being entirely filled with the cells, had become obliterated (Fig. 2). These masses of cells closely packed together had large and small, oval, vesicular nuclei, and bore a remarkable resemblance to nodes of squamous epithelium. The concentric arrangement of the cells was strongly suggestive of the beginning formation of epithelial pearls. At no point could the carcinomatous process be seen invading the uterine muscle. The cervical glands presented their usual appearance.



Fig. 3.—Photomicrograph of a cross-section of the left Fallopian tube showing three particles of the malignant tumor lying free in the lumen. (Hematoxylin and eosin; $\times 15$.)



Fig. 4.—Photomicrograph of the tumor particles shown in Fig. 3. The particles of the malignant growth are of the same histologic structure as the primary tumor of the endometrium (Fig. 2) and the metastasis to the cul-de-sac (Fig. 5). (Hematoxylin and eosin; $\times 70$.)

the internal os (Fig. 1). The neoplasm exhibited a high degree of differentiation. Some parts of the section presented a glandular appearance. Large and small groups of glands were seen. A gland was frequently separated from its neighbor by several layers of cylindrical epithelium, there being no intervening stroma. The gland cavities were lined by several layers of irregular cylindrical epithelial cells. The nuclei were oval, vesicular, and fairly uniform in size. There was no increase in chromatin, and only few if any mitotic figures were to be made out.

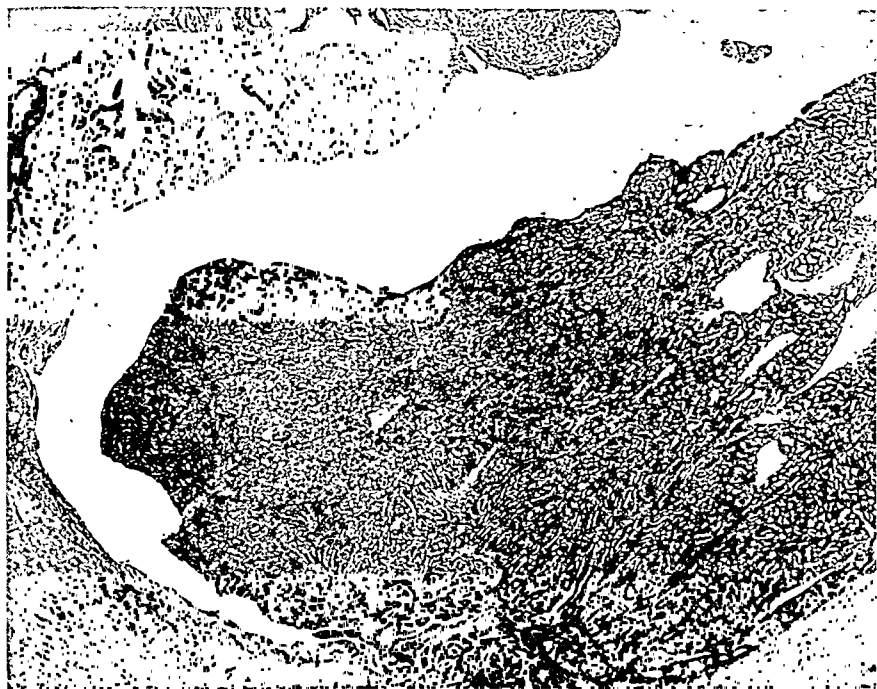


Fig. 1.—Photomicrograph of a section of the uterine tumor arising from the endometrium. (Hematoxylin and eosin; $\times 6$.)



Fig. 2.—Photomicrograph of carcinoma shown in Fig. 1. Typical papillary adenocarcinoma of the body of the uterus. (Hematoxylin-eosin; $\times 70$).

The tumor nodule removed from the posterior cul-de-sac presented a histologic structure of a well-differentiated glandular carcinoma, similar to that of the uterine growth as well as to the free tumor particles in the lumen of the tube (Fig. 5). The growth was found to be sharply demarcated from the surrounding tissue, although not definitely encapsulated. At the periphery and especially in the center of the nodule, numerous red blood clots were observed to contain spindle-shaped vacuoles due to cholesterol crystals, and needles of fatty acids. The tissue surrounding the tumor showed a marked small round cell infiltration.

Sections through the left ovary showed that the tissue was edematous, with chronic inflammatory changes, and diffusely infiltrated with fairly large, elongated oval to round cells (Fig. 6). At times, when grouped in masses, they were compressed into polygonal shape. At first, in the fresh state, the protoplasm seemed to be loaded with an abundance of small droplets of fatlike substance. Treated with ordinary reagents that dissolve out the fat (alcohol, xylene), the cytoplasm became a fine, areolar network, giving a foamy or highly vacuolated appearance. This impression was given support by the fact that abundant fatlike material was demonstrable in these cells by means of differential staining. The fatlike substances consisted of granules or round droplets, and at times crystals in small rods or fine needles united in clusters were seen. As far as could be made out by studying various stages of transition, these cells might arise from cells of the inflammatorily infiltrated connective tissue, and in a more advanced stage their cytoplasm was found to be increased. In the larger round cells, the cytoplasm became greatly diminished in amount and limited to small foamy rests; most of the nuclei had entirely disappeared. Those which remained, showed different stages of necrotic shrinkage, the nuclear material being condensed into a single round globule, staining uniformly and deeply with hematoxylin. These cells, showing fatty degeneration, represented the sequel and end product of a pathologic change, affecting the cells of the connective tissue. They may be considered as a distinct, pigment free type of cells of connective tissue origin, the pseudoxanthoma cells.

The cavity below the umbilicus was lined by inflammatory granulation tissue which, for the most part in its deeper portions, was also converted into masses of pseudoxanthoma cells, identical with those described in the left ovary. In a few places the tissue contained large areas of extensive necrosis with fragments of leucocytes which had undergone necrosis by karyokinesis.

Careful examination of numerous microscopic sections through the right ovary and the right Fallopian tube revealed no change but a few areas of round-celled infiltration. The right tube presented no carcinoma in its lumen, mucosa, veins, and lymphatics in any portion of the specimen.

We have in this case a typical papillary adenocarcinoma of the body of the uterus associated with a secondary growth in the posterior cul-de-sac. Bits of the malignant tumor were found free in the lumen of the left tube near its fimbriated end. The ovarian tumor and the umbilical nodule showed chronic inflammatory changes, extensive necrosis, masses of pseudoxanthoma cells, and the absence of carcinoma.

DISCUSSION

From a review of the literature, it would seem that the occasional finding of free and implanted cancer particles in the Fallopian tubes in cases of uterine and ovarian cancer is not as uncommon as was formerly believed. The supposed rarity of the condition is more apparent than real and may be due to a neglect in making routine microscopic examinations of the Fallopian tubes which, at the first sight, appear to be normal.

According to the reported cases, cancer cells and particles may enter the Fallopian tubes by either or both ends: (a) malignant material originating from ovarian and other intraperitoneal tumors may be wafted into the lumina of the tubes by their fimbrias; (b) cells and bits

The polypoid endometrial growth, occupying the uterine cavity, showed the histologic characteristics of a papillary adenocarcinoma, sometimes approaching the squamous cell type, identical in appearance with that of the endometrium.

The outer portion of the left Fallopian tube was moderately dilated, and its muscular layers were slightly thinned out. The mucosal folds were found to be normal. The most striking characteristics in the sections were three particles of carcinoma, having the same histologic structure as those of the endometrium and of the polypoid growth. They appeared to be free in the lumen of the Fallopian tube (Figs. 3 and 4). Carcinoma invading the mucosa itself could neither be determined in this Fallopian tube nor was it found in the veins or lymphatics in any portion of the specimen.

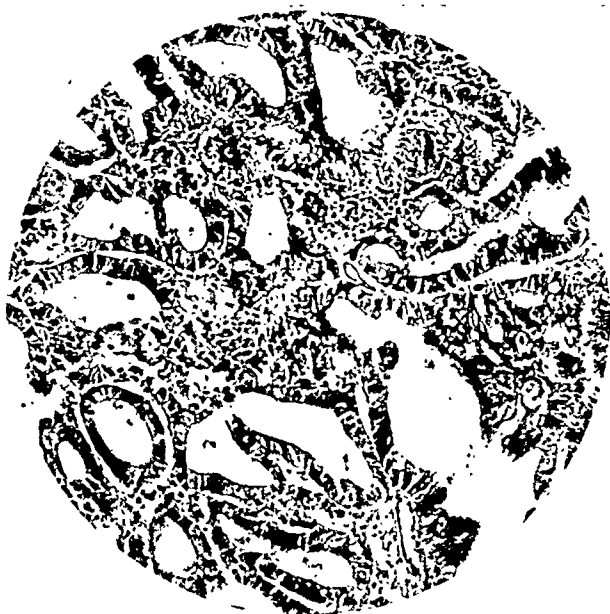


Fig. 5.—Photomicrograph showing a portion of the nodule removed from the cul-de-sac. The histologic structure is similar to that of the large uterine tumor (Fig. 2) and also to the particles of the tumor found free in the lumen of the left Fallopian tube (Fig. 4). (Hematoxylin and eosin; $\times 70$.)



Fig. 6.—Photomicrograph of a section of a portion of the left ovary. It shows well the foamy appearance of the pseudoxanthoma cells. (Hematoxylin and eosin; $\times 70$.)

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730 WEST CORNELIA AVENUE

THE ERYTHROCYTE SEDIMENTATION REACTION DURING PREGNANCY*

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THE sedimentation of erythrocytes is a characteristic of whole blood in both health and disease. The sedimentation rate is a means of expressing the velocity at which the red blood corpuscles separate from the blood plasma. The separation of these elements of the blood was noted in ancient times, and the knowledge of this property appeared in the writings of Galen. John Hunter, in 1855, noted the separation of the blood corpuscles from the blood plasma and recognized the increase in the rate of separation of these elements in disease. Robert Fahreus, in 1919, however, gave the first serious academic thought to the problem. It is interesting to note that his first observations on the sedimentation properties of red blood corpuscles were made during the natural course of pregnancy in an attempt to establish a laboratory test for the early diagnosis of pregnancy. Since this re-introduction to modern medicine, a vast amount of experimental and clinical work has been performed, and the results of this work dealing with the principles of erythrocyte sedimentation are worth stating.

THREE PHASES OF ERYTHROCYTE SEDIMENTATION

In the process of sedimentation three stages are commonly recognized. The initial stage, a period of aggregation, is one in which there is an agglutination of small groups of erythrocytes into rouleaux. This stage usually takes place during the first few minutes but is subject to variation. In extremely stable bloods, those in which the sedimentation will progress very slowly, the aggregation of cells proceeds slowly. In specimens in which a rapid sedimentation rate will be found, the aggregation

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from malignant tumors of the endometrium are forced into the uterine openings of the tubes by spontaneous, colicky contractions or manipulations of the uterus.

Spontaneous contractions of the uterus occur during menstruation and may also be caused by the stimulus of the pathologic uterine contents. Occlusion or narrowing of the internal os by the uterine growth or blood clots as well as retrodisplacement may assist in causing the backflow.

Manipulations of the uterus which may play a role in the intratubal spread of cancer include bimanual pelvic examination, intrauterine instrumentation as well as hysterectomy.

The further transportation of the malignant material within the lumen of the Fallopian tube occurs: (a) by the normal tubal peristalsis similar to the migration and final implantation of the fertilized ovum, being carried down the tubes toward the uterine cavity; (b) by antiperistaltic contractions of the tube passing cancer cells and tumor particles toward its fimbriated end, and at times, into the peritoneal cavity.

That the Fallopian tubes are capable of muscular contractions and peristaltic movements has been distinctly demonstrated by Rubin's peruterine gas insufflation and the kymograph.

Menstrual regurgitation of blood, containing malignant material and retrograde peristaltic movements in the Fallopian tubes should be regarded as noteworthy factors in causing this displacement, as about one-third of women suffering from carcinoma of the body of the uterus had not passed the menopause. 36.3 per cent of Stacy's cases¹⁰ were premenopausal; Norris and Dunne⁶ found 30.5 per cent; Masson and Gregg,⁴ 33 per cent. Crossen and Hobbs¹ observed that menstruation persists longer in women in whom carcinoma of the fundus develops. Furthermore, most patients having passed the menopause just before onset of symptoms are included in the postmenopausal group.

The implantation of cancer cells escaping from ovarian carcinoma upon the surface of the various structures in the pelvis is of common occurrence. The readiness with which particles of endometrial tumors may sometimes become implanted upon the tubal mucosa, the surface of the ovaries and the pelvic peritoneum has long been assumed by numerous authors but never until recently has this phenomenon been actually demonstrated. Careful microscopic investigations by Sampson disclosed the histogenesis and progression of these implants; their distribution was often found to be similar to that of the benign endometrial implants.

It is noteworthy to mention here that some danger exists in the spread of malignancy into the Fallopian tubes when such exists in the uterus when diagnostic and therapeutic manipulation and instrumentation are used.

CONCLUSIONS

1. The presence of free cancer particles in the normal Fallopian tube may indicate the pathway of spread of pelvic cancer.
2. A case is reported illustrating the spread of pelvic carcinoma by way of the Fallopian tube.

imposed graphs of the sedimentation rates in many instances augur recovery or remission. With a little experience the type of curve speaks for itself and no rate need be calculated. We believe that mere factual expression of a sedimentation rate based upon either one observation or upon the most rapid rate of fall within a narrowly delimited space of time is practically valueless clinically. We realize, however, that in the absence of graphic comparisons it is a necessary medium for the expression of the sedimentation rate.

SEDIMENTATION RATE AND BLOOD FIBRINOGEN

It would seem that there should be some quantitative chemicophysical change in one or more constituents of the blood responsible for the varying sedimentation rates. As has been stated, Fahreus considered the degree of aggregation of the erythrocytes directly related to the varying rates of fall. The radius of the corpuscles and their specific gravity as well as the specific gravity of the plasma is said to affect the rate. While there are many factors that may be considered, all investigators agree that the sedimentation of erythrocytes in whole blood is bound with the properties of the plasma alone. This is simply evidenced by crossing the clear plasma from a blood specimen in which there had been a rapid sedimentation rate and the washed cells from a specimen in which the rate was slow. The rate is invariably rapid. When the washed cells from the specimen with the rapid rate of fall are placed in the plasma from the "slow" specimen, the rate is slow. In the plasma most evidence points to the protein fractions as the responsible factors. Of these, the serum fibrinogen has been the most constant and reliable index. The serum globulin bears a close relationship with the fibrinogen and both are directly proportional to the sinking velocity of the erythrocytes while an inverse relation exists with the plasma albumin.

FACTORS CAUSING VARIABILITY IN READINGS

The technical procedures related to the sedimentation reaction are simple, but there are a few interesting experimental results which have a direct clinical bearing upon the validity of any observation. A knowledge of these should be familiar to anyone using this laboratory procedure. (1) Because of the changes that added electrolytes may bring about in the stability of the blood, Rourke and Plass deemed it advisable to determine the effects of the various anticoagulants in common use, in view of adopting a substance which had no effect upon the suspension stability of the blood other than to prevent the blood from clotting. Sodium fluoride (5 mg. per 5 c.c. of blood), potassium oxalate (14 mg. per 5 c.c.), potassium citrate (10 mg. per 5 c.c.), and 5 per cent sodium citrate (1:4) were found by them to produce slight slowing of the sedimentation rate in proportion to the concentration used, although these did not affect the trend of results. Heparin (1 mg. per 5 c.c. of blood) was found to be ideal, for the presence of more than sufficient quantities to prevent the blood from clotting did not further alter the rate of sedimentation. Other investigators, using smaller quantities of the electrolytic anticoagulants, separately or combined, found no appreciable variation in the rate. It would seem, therefore, that any of

of units can be directly observed. A parallelism, therefore, exists between the degree of aggregation and the sinking velocity of the red blood corpuscles. Fahreus stated in his original work that this was the most predominant factor in the sedimentation reaction. The period of aggregation has been explained on the basis of autoagglutination, various chemical changes in the blood, and electrophysical principles which I will not discuss at this time.

The second stage of the sedimentation reaction is the period of actual sedimentation. It is this stage which we commonly observe and record, and in which the variations noted in health and disease are characteristic.

The third stage is the period of packing. At this time the red blood corpuscles have progressively piled up upon each other. Active sedimentation has become arrested due to the passage of all of the corpuscles through the suspensoid. There is now practically complete separation of the blood plasma and the erythrocytes. At the end of this period the volume of cells closely approaches the volume following centrifuging. In blood specimens which are stable, there is usually a slow, constant rate of fall in which the separate stages cannot be recognized clearly and which may require several days before the packing period is reached. In these instances, when charted, the graph depicting the separation of the corpuscles from the plasma is a diagonal but straight line. In specimens having a rapid sedimentation rate there is usually a precipitous drop in the curve at the onset of active sedimentation and a rather abrupt horizontal swing when the period of packing begins. In the latter cases the period of packing usually begins prior to the customary hour's observation, and if the rate of fall is calculated upon this one observation alone, true results will not be obtained. The latter reading will be sufficient to reveal only that the rate is rapid by virtue of completion of the period of active sedimentation in one hour or less. In general, all rapidly falling specimens will tend to fall within a range, at the end of one hour, which is related to their actual cell volumes.

EXPRESSION OF SEDIMENTATION RATE

There are two common means of expressing the rate of sedimentation. The Westergren method expresses the rate in terms of millimeters per hour and only one reading is observed. In this method a 200 c.c. glass pipette having a 2.5 mm. internal bore (diameter) is used. The Cutler method expresses the rate in millimeters per minute. A 5 c.c. glass tube graduated in millimeters and having an internal bore of 15 mm. in diameter is used. Observations are made each five minutes for the duration of one hour, and a differential rate of fall is thus obtained. The period which is used as the criteria for the expression of the rate is that five-minute period in which the greatest actual fall takes place. This rate is then simply converted into millimeters per minute. Although the latter method requires constant attendance during the one hour period of observation, it has a distinct advantage: The most important phase of the sedimentation reaction is directly observed. By projecting the distance fall against the time interval upon a properly constructed chart the action of sedimentation becomes *graphic*. This we regard as most important. During the course of disease successive super-

progressively to an average fall of 45 mm. per hour at term. Our work does not reveal rates as rapid as these. Fig. 1 shows the average fall of all cases during the course of pregnancy. On this and subsequent graphs the time interval appears along the top of the graph and the number of millimeters' fall (degree of sedimentation) is denoted on the left. During the fifth month, there is an average fall of 14 mm. with a variation of 3.5 mm. (see Table I). During the sixth month, the fall varies between

TABLE I

DURATION OF PREGNANCY	AVERAGE SEDIMENTATION IN MILLIMETERS	VARIATION IN MILLIMETERS (PLUS OR MINUS)
5 mo.	14.0	3.5
6 mo.	19.0	4.0
7 mo.	22.0	3.0
8 mo.	22.5	3.5
Term	24.0	3.5
Second day post partum	27.5	9.0
Seventh day post partum	25.5	9.0
6 weeks post partum	12.0	20.0

17 and 21 mm. with an average of 19. During the seventh month between 20.5 and 23.5 mm., average 22; between 17 and 26 during the eighth month although the majority vary between 21 and 24.5, average 22.5 mm. At term the distance fall is between 22 and 25.5 mm. with an average of 24. As you will note by the curves representing the sinking velocity of the erythrocytes there is a progressive increase in the average rate of fall during the ante-partum course. In the majority of cases, the greatest activity occurs between ten and twenty minutes and varies between 2 and 4 mm.

Post partum, on the second day (Fig. 2), in many cases there is a sharp increase in the sedimentation rate although the average of all cases shows a further fairly even progression over the last ante-partum rate. There is little change on the seventh day after delivery although in all instances, barring complications, the actual one-hour fall is slightly less. The graph shows the distribution of the differential rates of fall. The average is 27.5 mm. per hour with a variation between 23 and 32. The distribution five days later shows little change. In both instances the curves show an early tendency toward the vertical and the three periods of the sedimentation reaction are more than suggested. The essential difference in the post-partum curve from the ante partum is due mainly to a more active fall in the early stages, in other words the period of active sedimentation takes place more promptly; the first stage, the period of aggregation of the erythrocytes, is more rapidly completed. In general, on the second and seventh post-partum days, the greatest actual fall per one five-minute period varies between 3 and 17 mm., but the greater proportion fall between 5 and 6 mm. This fall occurs during the ten- to fifteen-minute period although the most active period in many cases occurs in less than ten minutes.

In operative cases such as cesarean sections, the rate of fall is more rapid during the immediate post-partum course. This is probably related to the added trauma to the tissues. There is no consistent variation in the sedimentation rates in toxemias of pregnancy either ante or

the above-mentioned anticoagulants will not greatly affect the reliability of the sedimentation rate as far as clinical application is concerned. (2) Rourke and Plass found that after collection of a blood sample and after anticoagulants were added, if the specimen were permitted to stand at room temperature for six to twelve hours, there was no change in the rate of sedimentation after re-mixing. (3) With an increase in the temperature there is a corresponding increase in the sedimentation rate. However, within the range of normal room temperature (20° to 25° C.), there is not sufficient variation to necessitate correction. (4) A slight inclination of the sedimentation tube from the vertical will cause a great increase in the rate of fall. (5) Neither the bore of the tube nor the volume of blood used has any effect upon the sedimentation rate, provided the height of the column of blood remains the same. (6) There is no change in the rate after centrifuging blood to which an anticoagulant has been added and then re-mixing.

NORMAL VALUES FOR SEDIMENTATION RATES

The sedimentation of red blood corpuscles is a characteristic of normal blood which has slight physiologic variations in health and greater deviation in disease. The slowest rates are found with the blood of the newborn in which rates averaging 0.5 mm. per hour have been reported. In the normal healthy adult the ranges vary between 3 and 9 mm. per hour for men and from 3 to 13 in women although rates less than three are considered within the normal range but are uncommon. In most instances during disease, local or systemic, the variation from normal is marked. Physiologic increases in the rate of sedimentation have been observed and this occurs during pregnancy.

* * * * *

The work upon which this report on the sedimentation reaction during pregnancy is based was performed at Cleveland Maternity Hospital upon patients registered in the Maternity Hospital Out-Patient Department.* In performing the tests, 5 c.c. of whole blood were used to which three drops of a saturated solution of potassium oxalate were added as the anticoagulant. At the same time erythrocyte, leucocyte, and hemoglobin determinations were made. The Cutler 5 c.c. sedimentation tube was used and all actual observations were recorded on the Cutler graph at five-minute intervals for one hour. Theoretical corrections were based upon calculations of the cell volume, using a modification of the Rourke-Ernstine correction chart. In a few instances correction was based upon the percentage of normal erythrocyte count.

Inasmuch as most of the patients' first visit to the Maternity Clinic was rather late in the course of pregnancy, our studies have not been sufficiently complete prior to five months to report. However, from reliable reports in the literature the changes in the rate of sedimentation first occur during the latter part of the second month, and 99 per cent of all pregnant women have a definite increase in the third month. Fahreus' figures based upon 100 normal pregnant women show an average fall of 17 mm. per hour during the second month, 24 mm. during the third month, 29 mm. during the fifth month, and the rate thus increases

*Technical Assistance of Miss Rose Ketteringham.

post partum. Most acute infectious states, with or without a febrile reaction, are accompanied by an added increase in the rate of sedimentation during pregnancy. In many instances, however, cases which are obstetrically morbid are not associated with an increase in the normal expected sedimentation rate. These include morbidity due to cystitis, retained lochia, and common cold. Pyelitis, puerperal sepsis, and phlebitis are characterized by a rapid rate.

At the end of the puerperium, six weeks post partum, the rate of sedimentation again approaches normal. Seventy-two per cent are reported to have fallen within the normal range. In our series there is a wide variation, but the average fall at the termination of one hour is 12 mm., and there is the tendency of the projected graphs to assume a straight but diagonal line. This type of projection is a normal type or means a quiescent state in a previous infectious process.

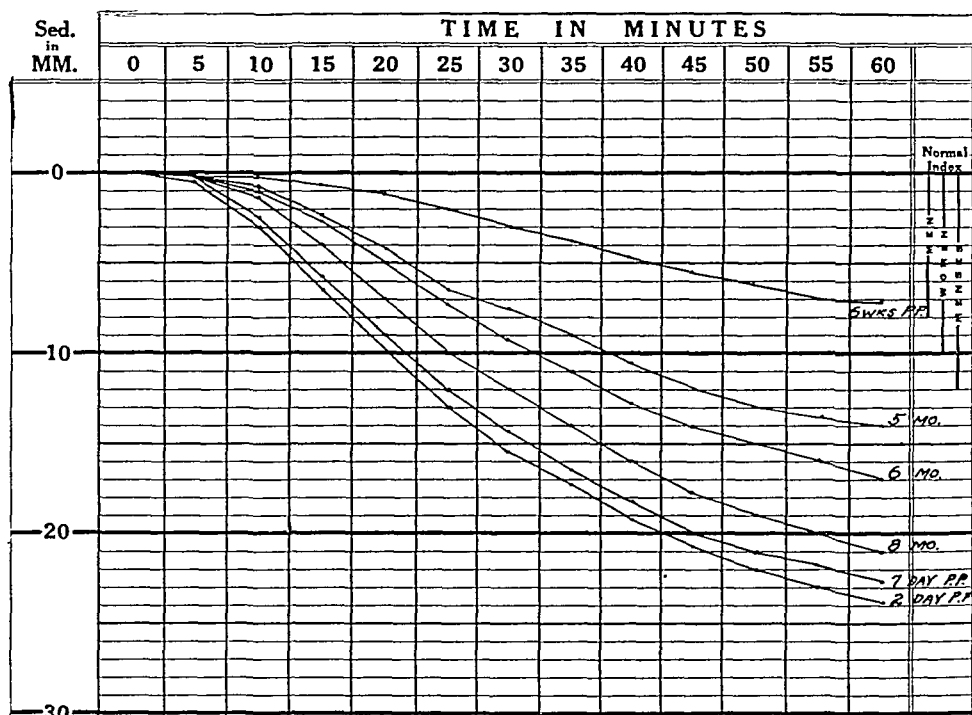


Fig. 3.—Sedimentation reaction during the course of normal pregnancy, one individual.

The rapid rate of the sedimentation of red blood corpuscles in pregnancy is said, by various investigators, to be due to a combination of factors: A physiologic leucocytosis produces an increase in the fibrinogen content of the blood; an anemia of pregnancy which is thought to facilitate an increase in the sinking velocity of the cells by virtue of the diminished number of particles in the suspensoid, therefore the mean *free* path of such particles becomes greater and consequently the rate at which they settle is increased. Other factors include: an increase in the blood volume, a decrease in the cell volume, and the absorption of the products of cell activity into the blood stream. Most reports are in accordance, however, no matter by what mechanism, that the rapid rate of

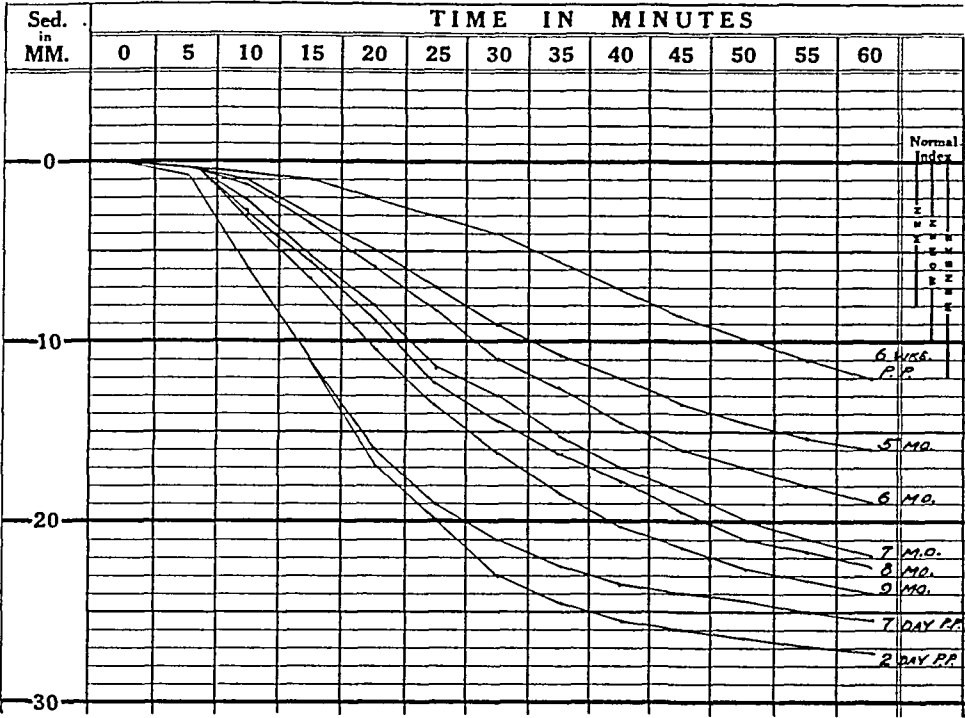


Fig. 1.—Average fall during pregnancy, actual.

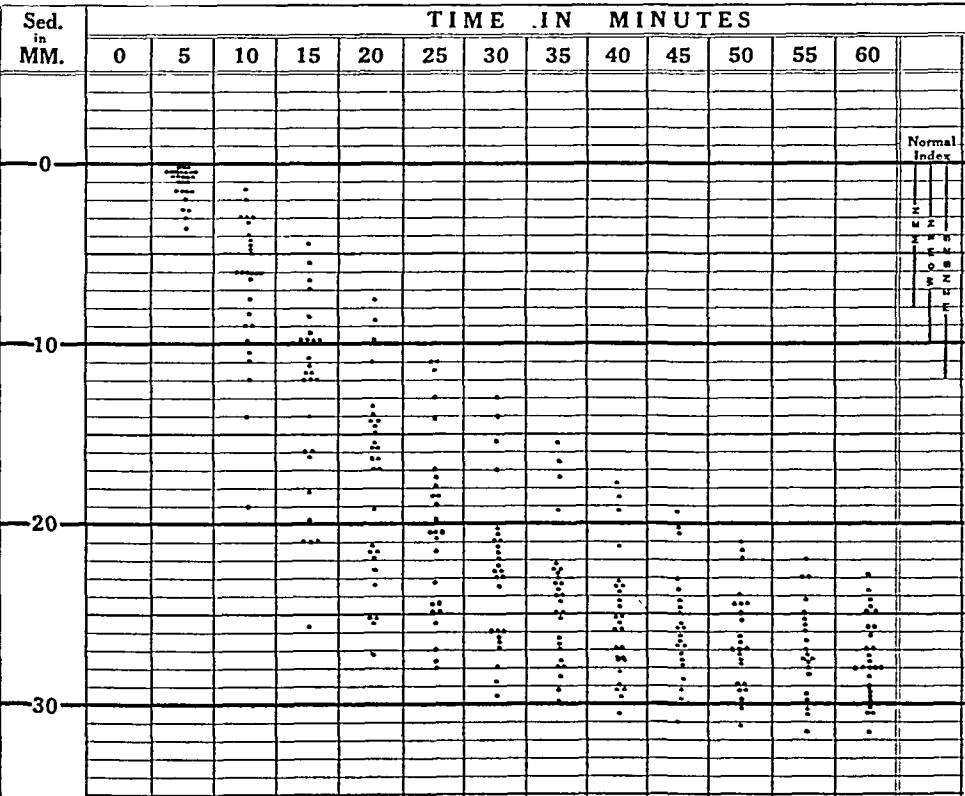


Fig. 2.—Distribution rates of fall, second post-partum day, actual.

sedimentation during pregnancy is related to a physiologic increase in the plasma fibrinogen, and in some instances this is as much as a thousandfold.

Fig. 3 illustrates the variation in the sedimentation rates during the course of pregnancy in one individual and serves to illustrate the value of graphic comparisons. I will not cite the leucocyte, erythrocyte, hemoglobin, and cell volume values which correspond to each curve, for I wish to discuss any relationship which might or might not be present later.

CORRECTION

In presenting the picture of the sedimentation reaction during pregnancy and the puerperium, it must be noted that all rates were actual and no reference was made regarding correction for anemia. The principle of any correction is based upon allowing for a variable item in order to state the results in terms of a normal constant. In the sedimentation reaction, corrections tend to aim at reducing an actual observation to an estimated value at a standard red blood corpuscle concentration in order to eliminate the variable factor, the degree of anemia. The cell volume has been used by most investigators in correcting sedimentation rates for anemia. In the normal individual there is supposedly a close correlation between the cell volume and the erythrocyte count, and the experimental error is but 0.5 per cent in the former and 5 per cent in the latter. By laboratory dilution experiments with normal bloods curves have been calculated and charts devised whereby the sedimentation rate of any blood specimen may be quickly corrected for anemia. The objection to these is that the normal range for cell volume varies widely among normal individuals. The variation is accentuated during pregnancy, and there is no constant reliable correlation between the erythrocyte count and the cell volume; a very slight tendency exists but no more. In most instances, for any one cell volume there is a variation of a million or more erythrocytes by count. Correlation between the cell volume and the hemoglobin content of the cells follows a slightly closer relationship but even here the average deviation for a given cell volume is 15 per cent hemoglobin. In fact during pregnancy there is no reliable relationship between the erythrocyte count and the hemoglobin content in the same specimen. The lack of actual correlation between any of the above variants therefore introduces three separate variables (cell volume, hemoglobin content, erythrocyte count) which should be taken into account for any reliable correction. Therefore, in an attempt to evaluate the efficacy of correction of actual sedimentation rates for anemia during pregnancy by one or all variable factors, we have been struck by the dissociation rather than the association of the elements concerned. We find that during pregnancy the value of corrected sedimentation rates in delivering a more accurate impression of the true trend of results is a misconception. Fig. 4 is a comparison of the actual and the corrected rates. The corrections were calculated from the cell volume. In most instances the corrections were carried out during the period of actual sedimentation only. The corrected rates at the end of

THE ROLE OF DEEP CAUTERIZATION IN THE PREVENTION OF CANCER OF THE CERVIX

A REPORT OF TEN THOUSAND CASES

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SINCE the publication of Hunner's¹ memorable paper in 1906, cauterization of the cervix for the treatment of chronic cervicitis has been practiced in our* Clinic.

TECHNIQUE

After trying different methods of cauterization Dr. Huggins and I, in 1914, began using consistently the present technique of deep cauterization of the cervix in our *operative* cases. The main purpose was the elimination of cervicitis, but the prevention of cancer, if possible by this means, was a strong motive in the program.

In 1924, I² published the technique of deep cauterization, the after-treatment, and some histologic observations. This is not an office procedure and is done under anesthesia, usually in conjunction with other operative procedures. Routine postoperative dilatations must be done for at least ten weeks after deep cauterization. Postoperative dilatations are not necessary when subtotal hysterectomy is done, but the cervix is permitted to heal with obliteration of the canal.

The serious results of cauterization of the cervix such as cellulitis, peritonitis, and so forth, which are stressed by some authors, have not been a serious problem in this series. They are due in most instances, I believe, first to incomplete cauterization, thereby leaving a zone of infected glands beneath the cauterized tissue (Fig. 2); second, to cauterization in the presence of unrecognized subacute or chronic infection of the upper genital tract; and third, failure to carry out the proper postoperative care.

Deep cauterization was selected because sections of the cervix showed that the inflammatory process is frequently deep seated and that it is necessary to cauterize deeply in order to eliminate it. In practicing deep cauterization some of the shortcomings of superficial cauterization are disclosed that are not generally known. In cervixes that have been cauterized superficially, sections taken immediately afterwards, or after healing has taken place, reveal too frequently that the deep glands have not been destroyed (Fig. 2) and that they are sealed in by the healing process and extensive cyst formation may result. In re-operating on these patients, it is found that many of these cervixes are riddled with cysts that are often not evident until deep incisions with the cautery blade are made, and mucus and mucopus are discharged. We use superficial cauterization only when we feel that the infection

*This paper is presented as a memorial to my former Chief, Dr. R. R. Huggins, who initiated and planned this survey which was made possible through the financial support of the Spang Cancer Research Fund. His untimely death occurred before it was well under way.

one hour do not give a true picture inasmuch as the period of packing had already begun and the results are therefore grouped into a smaller range.

Regarding correction I quote Fahreus: "A comparative investigation between the number of corpuscles and the sinking velocity carried out on a great number of clinical cases shows the concentration of the corpuscles to be of less importance than dilution experiments would lead one to suspect. There is a factor counteracting the rapid sinking in anemic conditions which probably stands in connection with the fact that the blood corpuscles have relatively less tendency to aggregate in the blood which is sparse in corpuscular elements. In other words, the disadvantage of cell dilution experiments is that there is no proof that in the body a change in the cell volume or cell count occurs without a simultaneous alteration in the plasma which might itself affect the sedimentation rate."

CONCLUSIONS

1. There is a progressive increase in the sedimentation rate during normal pregnancy. There is no alteration in this rate associated with toxemias of pregnancy.

2. During the puerperium the sedimentation rate returns to normal in approximately 75 per cent of cases and tends toward normal in the remainder. The change begins after the second post-partum day.

3. The increased sinking velocity of the erythrocytes during pregnancy is related to an increase in the plasma fibrinogen fraction of the blood.

4. Sedimentation is the result of the interplay between many forces and different factors may have importance in different cases so that the problems of correction for anemia are complex. We believe "the observed result is the true one and the calculated one is based on experiments which have only a presumptive counterpart in nature."

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11 per cent was the cancer confined to the cervix. In our series it was learned that there are no symptoms of early cancer, for many of these cases were hopeless when the first symptoms occurred. We stated at that time, thirteen years ago, that the hope of control of cancer of the cervix lay not in the method of treatment but in early diagnosis by periodic examination of women, and in the prevention of cancer by adequate treatment of the pre-existing lesion, chronic cervicitis. Or, even better, the prevention of cervicitis by the proper treatment of the cervix after delivery. That is still our belief.

It is our belief and experience that a cervix, healed and free of infected mucosa (Fig. 3) is no more liable to develop cancer than the surrounding vaginal mucosa.



Fig. 3.—Photomicrograph of a longitudinal section of the cervical canal healed after cauterization. Note absence of glands, and the presence of squamous epithelium which covers the lower portion of the cervical canal in the healing process.

In order to prevent cancer of the cervix, it was felt that an effort should be made to eliminate chronic infection and inflammation from the cervix, and that this was possible only by complete removal of the gland-bearing portion of the cervix or by its destruction by deep cauterization (Fig. 1). Deep cauterization is less time consuming than amputation of the cervix. It is a simple, rapid, bloodless method, and this is important in long gynecologic operations.

Since 1914 the cervix has been cauterized routinely in all operations for chronic tubal infection, for the cervix is usually the source of these infections; in all subtotal hysterectomies; and in all patients with cervical leucorrhea sufficient to warrant radical treatment. The oppor-

is superficial, as in the so-called congenital pseudoerosions, sterility, and eversions soon after the first delivery, for lacerations with eversion of mucosa then furnish conditions that predispose to infection, but cervicitis has not yet occurred or is only superficial.



Fig. 1.—Photomicrograph of a section of an erosion after deep cauterization. Note the destruction of the glands.



Fig. 2.—Photomicrograph of a section of an erosion after light cauterization. Note the zone of noncauterized glands beneath the cauterized zone.

RELATIONSHIP OF CHRONIC CERVICITIS TO CANCER

For years chronic infection has been thought to be a factor in the occurrence of cancer of the cervix, largely because of the high incidence of women who have borne children among those with this type of cancer. In an analysis of 150 cases of cancer of the cervix, in 1927, the author found that 92 per cent had borne children. In the same series, in only

one to twenty-four years. There were data on 771 subtotal hysterectomies.

In our follow-up cauterization series, the ages ranged from 19 to 77 years (Table II).

TABLE II. AGES OF PATIENTS AT TIME OF CAUTERIZATION AND AT TIME OF FOLLOW-UP SURVEY: 2,224 WOMEN TREATED BY DEEP CAUTERIZATION OF CERVIX UTERI, 1914 TO 1939

AGE-GROUP YEAR	NUMBER IN EACH AGE-GROUP	
	AT OPERATION	AT LAST OBSERVATION
14	3	0
15-19	75	13
20-24	268	105
25-29	406	263
30-34	451	345
35-39	413	424
40-44	318	381
45-49	165	309
50-54	91	212
55-59	22	115
60-64	8	38
65-69	3	15
70-74	1	3
75-79	0	1
All ages	2,224	2,224
Average age at operation		34.6 years
Average age at last observation		40.1 years
Average period of observation		5.6 years

In the 10,000 series before the follow-up study was made, 2 patients were known to have developed cancer of the cervix (Cases 1 and 2). In the 31.4 per cent follow-up, or 3,143 patients, no additional cases of cancer of the cervix were found. Of the patients 73½ per cent were operated on by Dr. Huggins and myself by a technique that is quite constant. No case of cancer is known to have occurred in these patients. The 2 known cases of cancer developed in the remaining 26½ per cent operated upon by twenty-four other surgeons. Ten of these surgeons received their training with us, and the others are now practicing a similar technique, so that it is very unlikely that more than a small percentage of these cervixes were cauterized less extensively than we practice. But there is some evidence that one of the two cancers which developed falls into this small percentage. This might indicate that superficial cauterization is less effective than deep cauterization as a prophylactic procedure. No such conclusion would be warranted, however, without a comparable series and follow-up of cervixes superficially cauterized, for Holden¹⁰ states that neither he nor Dickinson has seen a case of cancer develop after office cauterization.

DISCUSSION OF SURVEY

In order to determine the true prophylactic value of deep cauterization in this series, it is necessary to find out what should be the incidence of cancer in 10,000 gynecologic patients who have had no treatment of the cervix and who have been followed for years. No reliable figures of the incidence of cancer of the cervix in women in general are available.

But certain estimates can be made from isolated surveys and published

tunity was used to clean up the infected cervix in any patient on whom operation was necessary for other conditions (Table I).

TABLE I. TYPE OF OPERATIONS

Cauterization alone	335
Cauterization and radium (in uterine cavity)	120
Cauterization and plastic surgery	629
Cauterization, plastic surgery, and laparotomy	323
Cauterization and laparotomy (other than hysterectomy)	1071
Cauterization and hysterectomy (subtotal)	665

CANCER OF THE CERVICAL STUMP

It has been found by many observers that cancer of the stump of the cervix after subtotal hysterectomy constitutes 2 to 5 per cent of all carcinomas of the cervix. In our 150 cases, there were four, or 2.66 per cent. This does not give any idea of what percentage of cervical stumps will develop cancer. Neilson³ reports that statistics in 17,139 cases of subtotal hysterectomy show subsequent stump cancer in 67, or 0.39 per cent. He states that the incidence may be 1 to 1.5 per cent.

The increased mortality of total hysterectomy throughout the country will more than counterbalance the loss of patients from cancer of the cervical stump. The technique of subtotal hysterectomy, as I⁴ advocated in 1926, consists of deep cauterization of the cervix regardless of whether it appears normal or not, followed immediately by laparotomy and subtotal hysterectomy. The supravaginal amputation is made low down near the attachment of the sacrouterine ligaments, and crosses the cauterized and sterilized cervical canal. Thus the cervical mucosa is destroyed, the canal is sterilized, hysterectomy is made safer and future trouble with the stump is practically eliminated. To cauterize or cone out the cervical canal from within the abdomen, as practiced in some sections, is not sufficient, for cancer usually occurs in the erosions or at the junction of the squamous and columnar epithelium on the portio.

SURVEY

In 1929, Dr. Huggins⁵ reported 2,985 of our cauterization cases, with no knowledge, up to that time, of the development of cancer of the cervix in any of these patients, but no follow-up study had been made. In the same year, Pemberton and Smith⁶ reported that in 5,952 operations on the cervix, including 1,408 cauterizations, 5 cases of cancer had developed and none had occurred in the cauterization group. (Only 20 per cent of their total series were followed either by letter or examination.)

Deep cauterization has been gradually adopted by those in the Gynecological and Obstetrical Departments of the University of Pittsburgh Hospitals. There is now a series of 10,000 cases over a period of twenty-five years. A follow-up study was undertaken to determine the incidence of cancer in the cervixes so treated.

RESULTS OF SURVEY

Data were secured concerning 3,143 patients, and 1,341 of them returned for examination. The time interval after cauterization was from

TABLE III. EXPECTED AND OBSERVED DEATHS FROM ALL CAUSES AND FROM CANCER OF THE UTERUS AMONG 3,143 WOMEN FOLLOWED FOR VARYING PERIODS AFTER DEEP CAUTERIZATION OF THE CERVIX

	NUMBER OF PA- TIENTS	DEATHS FROM ALL CAUSES			DEATHS FROM CANCER UTERUS		RATIO	OBSERVED
		OBSERVED		EX- PECTED†	OB- SERVED	EX- PECTED†		EXPECTED
		NUM- BER	PER CENT	NUM- BER			DEATHS FROM	
							ALL CAUSES	CANCER UTERUS
Age known	2,224	58	2.6	102	2	4	0.57	0.50
Age unknown	919	21	2.3	42*	0	2*	0.50	---
Total	3,143	79	2.5	144	2	6	0.55	0.33

*Deaths expected in group with age unknown on assumption of same experience as that in group with age known.

†Deaths expected on basis of age-specific mortality among all females, Pittsburgh, 1930.

Although no other cases of cancer were found in this survey it is evident from Levin's studies that the survey covered predominantly patients who were in an age group in which cancer of the cervix is not common, for the average age of the follow-up series was 40 years, and in our cancer of the cervix series, 69 per cent occurred in patients over forty years of age. It is stated that ten to fifteen years of chronic irritation seems to be necessary before cancer of the cervix develops, and our follow-up averaged only 5.6 years. This means that most of the patients in our follow-up cases were operated upon in the last five to fifteen years. This would be expected, as the longer the time interval after operation the more likely it is that the patient is lost through change of address, etc.

Levin feels that this study does not disprove the clinical impressions and statistical evidence that chronic cervicitis is a causative factor in cancer of the cervix and that the elimination of chronic cervicitis will prevent cancer. He found our incidence very low as compared to other statistics but that our follow-up study covered only to the lower limits of the age groups where the incidence of cancer rises rapidly. A few more years of observation of this group should give very definite information. He feels also that his estimates were based on women in general, while our series consists of women who came for gynecologic treatment and that due allowance should be made for this factor.

If the group that we contacted can be followed for another five or ten years, the question should be settled definitely. We intend to carry it on in our Department and with a more intensive effort to contact those patients who were operated upon more than five or ten years ago.

The recorded incidence of cancer of the stump is also higher than in women in general. Dr. Huggins and I have done 2,525 subtotal hysterectomies with cauterization of the cervix. They are included in the 10,000 series and information was obtained on 506 of them in the follow-up study. We know of no instance of cancer of the stump in this group. If Neilson's³ estimate of approximately 1 per cent is correct, there should develop 25 cases in our hysterectomy series.

statistics. In the first examination of 1,200 women in general who volunteered for a program of periodic examination, Catherine Macfarlane⁷ found 3 cases of unsuspected cancer of the cervix, an incidence of 0.25 per cent. An average of six similar figures from different sources would seem to place the incidence of cancer in women in general at approximately 0.19 per cent.

If this incidence were applied to our 10,000 series there would be 19 cases of cervical cancer at any one time.

Our patients were gynecologic cases, and in gynecologic cases and in those followed over a period of years, the incidence is much higher, for Meigs⁸ cites a ten-year follow-up by Woolston of 1,014 patients who had had a repair of the cervix. It disclosed the fact that 1.87 per cent probably developed cancer of the cervix from six to twenty-nine years after operation. This corresponds quite well with the incidence in gynecologic cases in hospitals. An average of three such figures gives an incidence of 1.82 per cent. This incidence applied to the 10,000 series would be 182 cancers.

The true incidence would probably lie between these two figures, 19 cases for 10,000 women in general, and 182 cases in 10,000 gynecologic cases. Levin⁹ who has done notable statistical work on cancer is more specific in his estimates. He approached the problem in a new and different manner, and by applying accurate and scientific statistical methods to our data, estimated the expected incidence of cancer in the various age groups. This is a very valuable contribution to statistical methods for similar surveys in the future. He writes as follows:

Among 3,143 women followed for varying periods after deep cauterization of the cervix by Dr. Cashman and his associates, there were observed 79 deaths from all causes. In 2,224 of these patients, the average age at the time of cauterization was 34.6 years and the average age at the time of death or last observation was 40.1 years. The average period of observation was 5.6 years (Table II).

The expected number of deaths from all causes and from uterine cancer in this group were calculated by applying to each age-group for the period of observation the mortality rates among females in Pittsburgh for the census year 1930 (Table III). It was found that during the period observed only 6 deaths from cancer of the uterus would be expected in the 3,143 patients, whereas two occurred.

It is, therefore, at once clear that these patients have not been followed long enough to test adequately whether or not they will remain comparatively free from subsequent development of uterine cancer. This point may be amplified by citing the fact that if the entire group, 3,143, were observed from the time of cauterization until all had died, the number of deaths from uterine cancer which would be expected to occur is 79. The period of actual observation, however, was such that only 6 deaths might be expected. Even if we disregard the fact that only 55 per cent of the expected deaths from all causes were observed, the difference between 6 and 2 deaths in a sample of this size cannot be considered significant.

On the basis of this material I would, therefore, conclude first, that the number of patients followed and the average duration of the follow-up was too small to constitute a fair test of the value of cauterization of the cervix in preventing subsequent development of carcinoma; and, second, that as far as the facts obtained *in this survey* go, they do not indicate that cauterization has any prophylactic value. In view of the importance of settling this question, it is to be hoped that Dr. Cashman will continue his investigation by continued follow-up of these patients.

6. A follow-up study was carried out but the average time interval after cauterization was only 5.6 years and the average age of the patient 40 years. The results therefore fail to show any very marked reduction in the incidence of cancer in the group followed, for by a new application of a statistical method to our series of 3,143 followed patients, Levin estimates the expected incidence as only 6 deaths from cancer of the uterus in the time observed. Two deaths are known to have occurred and one of these was from cancer of the cervix. A longer follow-up study will be necessary before definite information can be given.

7. Deep cauterization and subtotal hysterectomy has made total hysterectomy unnecessary for benign conditions of the uterus.

I wish to express appreciation to the members of the Gynecological and Obstetrical Staffs of the Elizabeth Steel Magee and St. Francis Hospitals, Pittsburgh, Pennsylvania, for their cooperation in permitting and aiding in the survey on their patients; to Dr. Mortimer Cohen, Dr. Albert Bruecken, Dr. John Frank, and Miss Anne Shiras for the pathologic sections, photomicrographs, color photography, and lantern slides; and Miss Theresa Mayer and Mrs. Betty Neeld for their seemingly endless work in trying to contact these patients and record the results in various ways.

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THE RATE OF ENTRANCE OF AMNIOTIC FLUID INTO THE PULMONARY ALVEOLI DURING FETAL RESPIRATION*

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THE present investigation is an attempt to determine the extent to which the respiratory movements of the fetus function to promote a tidal flow of fluid between the amniotic sac and the alveoli of the lungs.

The question as to whether or not the amniotic fluid normally enters the lungs during intrauterine life was raised long ago by Ahlfeld in connection with his observations of rhythmical excursions of the abdominal wall of women near term, which movements he described as evidence of respiratory excursions of the chest wall of the fetus. Ahlfeld expressed the view that amniotic fluid did not enter the fetal lungs.

A second type of evidence bearing upon this question has accumulated, namely, the finding of amniotic sac contents in the lungs of infants at autopsy.

*Presented at a meeting of the Chicago Gynecological Society, May 17, 1940.

COMMENT

Perhaps there is no method of preventing cancer of the cervix 100 per cent, but in our personal series we have been unable to find a single case in spite of an honest effort at follow-up. A larger series of cases, or a longer period of time and a better follow-up may change that report. Even so, if it is shown that the incidence of cancer has been much reduced, the work has been worthwhile. It is much more satisfactory than the cure of an equal number of cancers of the cervix, for many of the cancer-cured cases are uncomfortable and unhappy; uncomfortable from undesirable radiation effects; and unhappy because of the dread of recurrence. Our interest has been in the prevention, rather than the cure of cancer of the cervix in the advanced stages in which it is usually seen today.

There were 25.4 per cent of the patients in our cancer series who had had pelvic operations, and one-half of them within five years before they reported with cancer. No prophylactic treatment of the cervix had been done, and the opportunity for the prevention of cancer had been lost.

The chief disadvantage of deep cauterization is the necessity for the irksome postoperative dilatations, but if the patient is completely relieved of cervicitis and if cancer is prevented, it is worth the effort. Before the advent of radium, the cautery was a valuable agent in the treatment of cancer of the cervix. It should be more effective before the onset of cancer.

In such a series, it may be that occasionally an incipient cancer, too small to be even suspected on gross examination, has been destroyed by the cauterization.

Prevention of cancer of the cervix, by any method that is effective, is advocated in this paper. Deep cauterization has been the method used in this series because it can be quickly done along with other operative procedures, and sections show that it is effective in eliminating cervicitis.

CONCLUSIONS

1. Chronic cervicitis seems to be a contributing factor in the causation of carcinoma of the cervix.

2. Cancer of the cervix is insidious in onset and because of the late stages in which it is seen today, prevention of cervicitis, prevention of cancer by adequate treatment of existing cervicitis, and early diagnosis by periodic examination of women over 25 years of age, offer the best solution of the problem.

3. In order to destroy infection in the cervix by cauterization it is often necessary to cauterize deeply and extensively.

4. Careful postoperative care is necessary to prevent stenosis of the cervical canal after deep cauterization.

5. As far as we know, deep cauterization of the cervix has been an effective method of preventing cancer in our series of 10,000 cases, for only 2 cases of cancer of the cervix are known to have occurred in this series.

litter were observed following injection of India ink within the amniotic sac. Pentobarbital sodium was injected directly into the fetus for the suppression of respiratory movements.

The present observations are based upon 30 fetuses obtained from 10 rabbits at term. Seventeen fetuses were breathing at the time of injection of the amniotic sac while 13 were apneic.



Fig. 1.—*A*, Lung of rabbit fetus breathing within the uterus obtained three minutes after injection of India ink into the amniotic fluid. *B*, Lung of apneic fetus obtained twenty minutes after injection of sac. In both fetuses 1 c.c. of India ink was introduced into the amniotic fluid. Entrance of stained fluid in *A* and the absence of it in *B* demonstrated that intrauterine respiratory movements result in the breathing of amniotic fluid.

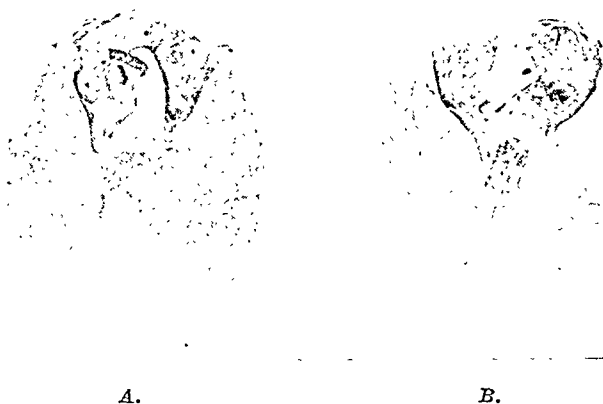


Fig. 2.—*A*, Lung of rabbit fetus breathing within the uterus obtained one minute after injection of India ink into the amniotic fluid. *B*, Lung of apneic fetus.

OBSERVATIONS

The entrance of blackened amniotic fluid into the lungs of fetuses which showed respiratory movements was regularly observed. In contrast, in apneic littermates the lungs failed to show carbon particles despite immersion of the fetuses in ink-stained fluid. It is evident that the intrauterine movements of the chest and diaphragm function to promote a tidal flow of fluid between the amniotic sac and the alveoli of the lungs. Evidence of the magnitude of the tidal exchange is afforded

Farber and Sweet found cellular debris characteristic of amniotic fluid in 88 per cent of the lungs of infants which survived two hours to five weeks after birth in a series of 124 cases. More recently, Camerer found constituents of amniotic fluid in the lungs of all cases except three in a series of 212 autopsies which included 93 stillborn and 119 infants that died within one hour to one week after birth. Furthermore, extensive pneumonia in stillborn babies and those succumbing soon after birth has been noted with increasing frequency as microscopic examination of the lungs has been made (McGrath and Kuder, 1936; Chase, 1935; Warwick, 1934; Cruickshank, 1930; Hook and Katz, 1928; Johnson and Meyer, 1925; Browne, 1922; Slemons, 1915). For instance, Johnson and Meyer found evidence of pneumonia in 97 cases of a series of 500 consecutive autopsies at the Sloane Hospital, and in 68 of these it seemed probable that infection occurred before birth.

Additional evidence of the entrance of amniotic fluid into the lungs before birth has been obtained by x-ray of the fetus following injection of the amniotic fluid with thorotrast.

Observations have been made in women (Ehrhardt, 1938; Reifferscheid and Schmiemann, 1939) and in guinea pigs (Windle, 1939). Ehrhardt noted aspiration of amniotic fluid by a fetus of 20 cm. length or four to five months' development. Reifferscheid and Schmiemann reported similar results. Numerous sources of error inherent in the thorotrast method and resulting in failure to obtain x-ray evidence of its presence were pointed out by Ehrhardt in a careful study in women and laboratory animals.

A new approach to the problem is afforded by the recent development of an experimental method which permits direct observation of fetuses showing rhythmical respiratory movements within the unopened uterus (Snyder and Rosenfeld, 1937). By the addition of foreign substance like carbon particles of India ink, the amniotic fluid may be readily stained and then traced in various parts of the respiratory passages. It is possible to see and count the intrauterine respiratory excursions. Thus, for the first time in fetuses under direct observation showing rhythmical breathing for many hours, one may determine whether or not fetal respiratory movements result in the entrance of amniotic fluid into the lungs. Evidence of the rate of exchange between the amniotic sac and the pulmonary alveoli is obtained by sacrifice of breathing fetuses at various intervals after injection of the amniotic sac.

METHOD AND MATERIAL

In a typical experiment a rabbit at full term, i.e., 32 days, was selected for observation. Inhibition of labor was assured by the induction of ovulation a week before term, i.e., at 25 days, by the injection of 100 rat units of extract of urine of pregnancy, antuitrin-S (Parke, Davis and Company). Inspection of the animal's abdomen showed localized rhythmical movements which were transmitted from fetuses at various sites where the uterus was in direct contact with the abdominal wall. The respiratory rate of various fetuses could readily be counted. In order to permit laparotomy and at the same time to avoid the effect upon the fetuses of a general anesthetic, the spinal cord was sectioned at the lumbar level. The uterus was exposed by laparotomy carried out beneath the surface of a large bath of Ringer's solution at 37° C. The fetal respiratory movements were easily observed directly through the thin uterine wall. The rate of the excursions was noted. In order to stain the amniotic fluid, 1 c.c. of 50 per cent India ink was introduced within the amniotic sac in the dorsal neck region between the ears. Discoloration of the entire sac was almost immediately evident. After intervals which ranged from one minute to many hours the trachea was closed by clamping the neck of the fetus. As a control, apneic fetuses of the same

not found in lungs of apneic ones. In the brief period of a minute of intrauterine respiratory activity, there is a striking flow into the pulmonary alveoli of the fluid in which the fetus is immersed.

The presence of amniotic fluid in the lungs and its tidal flow during normal fetal life afford a basis for tracing the origin of damage to the future air passages.

In so far as there is obscurity regarding the mechanism whereby extensive injury of the lungs occurs before birth, even resulting in intrauterine death associated with pneumonia, it is apparent that the present findings provide a new link in the chain of evidence, by which intrauterine pneumonia is connected with abnormality of the amniotic fluid.

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DISCUSSION

DR. W. F. WINDLE.—We have confirmed Dr. Snyder's factual observations. However, I must disagree with some of the interpretations he has placed upon them.

The physiology of respiration in the fetus in utero is not so greatly different from that of the newborn infant or even of the adult as it might seem. If it is to be understood clearly it should be viewed in the light of at least three fundamental concepts.

I. A respiratory center develops in the embryo, reaching a functional state as early as the twelfth week in man. This center seems to be inactive but can be activated by (a) afferent nervous impulses discharging into it, (b) by the chemical agent, carbon dioxide, acting upon it directly, or (c) by anoxial enhancement of its excitability (lowering its threshold). It is doubtful if the fetal respiratory mechanism actually functions in the strictly normal course of intrauterine existence; its threshold is very high. The fetal respiratory mechanism is a dormant system charged with potentialities, long in advance of the time it can be of any use.

II. The mammalian fetus does not thrive on venous blood, as commonly taught. It receives well-oxygenated blood from the placenta, and this blood reaches the fetal brain without great loss of oxygen. It has been proved in the sheep that the umbilical vein blood is 90 to 95 per cent saturated throughout a fair portion of the gestation period. The fetal carotid artery blood is as much as 88 per cent saturated with oxygen. In the last days of gestation the values decline somewhat, and a physiologic partial anoxemia becomes established. This is by no means an asphyxia. Some confirmatory data are available for man.

III. The fetus in utero is hypotonic if not actually atonic. It appears to lack a well-developed mechanism to return its blood to the heart. The uterine musculature substitutes for this lack of tonus, and rhythmical prelabor uterine activity assists in returning blood to the fetal heart. In some species of animals, notably the cat, each uterine contraction sends a freshet of well-oxygenated blood to the fetus. In late pregnancy each uterine relaxation allows a partial anoxemia

by comparison of lungs which were obtained from fetuses at various intervals following injection of the amniotic sac with ink. Thus, in littermates which were breathing at the rate of 28 per minute, the trachea was clamped three minutes following injection of the amniotic sac of one fetus and one minute after similar injection of a second fetus. The extensive blackening of the lungs of the first one shows the rapidity of entrance of the dark-colored amniotic fluid into the fetal air passages (Fig. 1). In the second fetus much less carbon is to be seen although scattered black areas are clearly evident in the lungs even within one minute after staining of the amniotic fluid (Fig. 2). The findings are confirmed by microscopic examination. Carbon particles are found in the pulmonary alveoli and large air passages throughout the lungs.

Furthermore, in various fetuses of the same litter which were breathing at different rates, it was noted that the lungs were darker in those which showed the greater respiratory activity. For instance, in a fetus breathing at the rate of 96 per minute for five minutes after addition of 1 c.c. of ink to the amniotic fluid, the lungs were much darker than those of a littermate removed after sixteen minutes of breathing ink-stained fluid at the rate of 10 per minute.

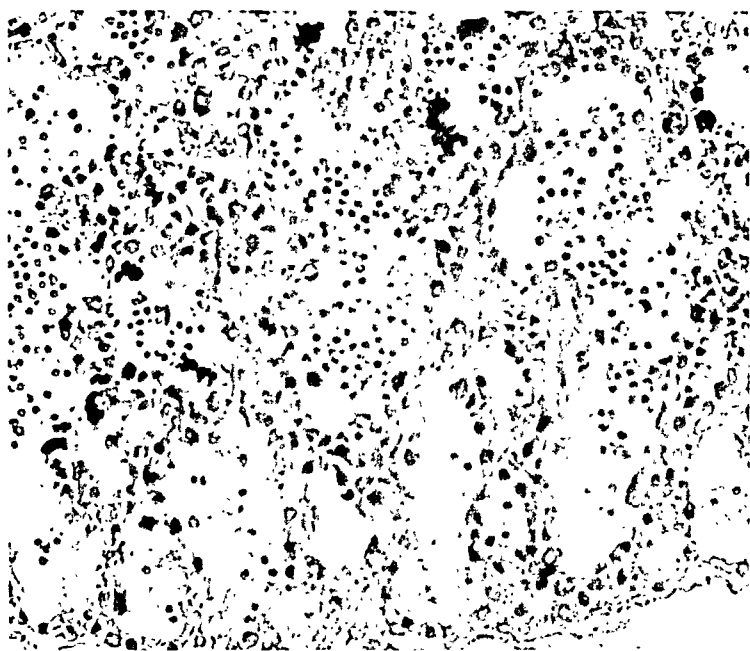


Fig. 3.—Lung of rabbit fetus stillborn following contamination of the amniotic fluid with blood. The pulmonary alveoli contain blood cells.

In Fig. 3 is shown the lung of a rabbit which died undelivered at full term. At autopsy the amniotic fluid was conspicuously stained with blood. Microscopic examination of the lungs revealed the presence of blood uniformly distributed throughout both lungs. Contamination of the amniotic fluid was associated with accidental hemorrhage of the placenta.

SUMMARY

From the foregoing experiments, it is evident that ink-stained amniotic fluid promptly enters the pulmonary alveoli of breathing fetuses but is

of the contraction, the placenta being more or less compressed, and then as the uterus relaxes the heart becomes more rapid. I would like to have Dr. Windle tell us if the heart rate slows with each contraction because of excess blood supply and oxygen or because of asphyxia.

Another thought is that, assuming intrauterine respiration, the fetus at birth carries with it from the uterine cavity a certain quantity of amniotic fluid in each of the alveoli even though the alveoli after birth are somewhat distended by air added to their content. Unless that residual amniotic fluid is rapidly absorbed by the epithelium of the alveoli, it should make its appearance from the lungs and out through the mouth and nose of the newborn infant. We do see newborn infants whose pharynx and trachea are filled with amniotic fluid, blood, meconium, etc., but the infant who cries lustily at birth does not have the sound of a child whose lungs are partly filled with amniotic fluid.

DR. SNYDER (closing).—Regarding Dr. Windle's anatomic observations in guinea pigs, it is interesting that aspiration of thorotrast was revealed by x-ray in certain fetuses but not in all cases. In this connection, Ehrhardt pointed out in his last paper (1939) that the presence of thorotrast in amniotic fluid or in the gastrointestinal tract may escape detection by x-ray. Thus, in mice drinking a diluted solution of thorotrast for several days, no x-ray evidence of its presence was obtained; however, after an additional period of days a definite shadow in the gastrointestinal tract was obtained, indicating a separation of thorium and the diluting medium probably by the intestinal epithelium. Similarly after injection of the amniotic fluid with thorotrast, various intervals, for example seventy-two hours, elapsed before a shadow appeared in the respiratory tract. Ehrhardt concluded that the mechanism for separation or concentration of thorium was even less effective in the respiratory passages than in the intestinal tract.

The various other problems which were raised require separate answers. Regarding such a question, for example, as the nature of the chemical regulation of fetal respiration, it would seem that Dr. Windle's conclusions do not always take into account all of the available data.

In connection with Dr. Baer's point concerning the absorption of fluid from the lungs, it is interesting to recall the structure of the pulmonary alveoli. Bloom's investigations have shown that it is difficult to demonstrate a continuous epithelial lining, the capillaries appearing to be uncovered. The morphologic barrier to exchange between the lumen of the alveolus and the blood stream is thus reduced to a minimum.

Trussell, Ray E.: Hypersensitivity as a Factor in Chronic Monilia Vaginitis, J. Iowa M. Soc. 29: 485, 1939.

It is now well established that a marked growth of yeastlike fungi in the vagina, particularly in pregnant and diabetic women, may produce acute vaginitis. Such patients are usually treated satisfactorily with gentian violet, but even if untreated, some experience spontaneous cure with termination of the pregnancy or after control of the diabetes.

In contrast to this type of severe vaginitis which is encountered only occasionally, it is common to see women who complain only of vaginal and vulval itching and in whom cultures reveal no commonly recognized vaginal pathogens except a few "monilia." Such infections are at times refractory to the usual fungicides and the itching and low grade inflammation persist.

Recently it has been suggested that certain of these women are hypersensitive to the fungi and that the itching and mild inflammation are manifestations of a local allergic reaction.

Ray E. Trussell tested 200 pregnant women and found that a large percentage of adult women are skin sensitive to commercial oidiomycin. It would appear that the use of this fungus extract for skin tests would be of limited value in indicating suitable cases for desensitization of patients with chronic monilia vaginitis on the theory that the condition may be on an allergic basis unless focal flare-ups or skin reactions stronger than normal can be shown to occur consistently.

J. P. GREENHILL.

to manifest itself in the fetal brain, and fetal activity ensues in consequence, only to subside again with the succeeding uterine contraction.

Keeping these concepts in mind let us examine the question of fetal respiratory movements and aspiration of amniotic fluid. Under experimental conditions which interfere in any way with normal oxygenation of the fetal brain, it is very easy to obtain rhythmical movements which are not present normally in fetuses. In Dr. Snyder's experiments the normal uterine motility had been inhibited hormonally. This may have impaired the mechanism which returns blood to the fetal heart and may have allowed an anoxemia to be set up in the fetal brain. Anoxemia affects the fetal respiratory center, lowering its threshold to a point which can be reached by the usual stimulatory agent, carbon dioxide. Had Dr. Snyder obtained blood gas analyses in his specimens, I am confident he would have found very little oxygen in the fetal blood. We have done that in the cat and I can say that fetal quiescence and apnea (true physiologic apnea, not asphyxial apnea) are associated with values in excess of 50 per cent saturation, rapid rhythms of respiratory movements with values between about 25 and 50 per cent saturation, and slow dyspneic rhythms with values well below 25 per cent saturation with oxygen. In fact the gasping movements persist when the fetal blood contains less than one-half a volume of oxygen per cent.

In late prenatal life when the placenta may be said to have undergone some physiologic deterioration, the rapidly growing fetus is hard pressed to get enough oxygen. With each uterine relaxation, the fetus becomes active and may even exhibit some rapid respiratory rhythms. Such movements may occur occasionally in the human being near term, but their incidence is certainly not great, and it is not proved that they occur in all.

Even if these fetal respiratory rhythms are truly of normal occurrence, which may still be questioned, do they result in aspiration of the amniotic fluid? In the absence of muscle tonus, a negative intrathoracic pressure does not manifest itself. The normal fetus is hypotonic if not actually atonic.

We have proved that aspiration of amniotic fluid can occur in fetal guinea pigs, but only under asphyxial conditions. Thorotrast was introduced into the amniotic sacs of 27 fetuses without anesthetizing the pregnant animals; normal physiologic conditions were maintained. Roentgenograms taken within a few minutes, a few hours, and at daily intervals until birth revealed that this material entered the fetal lungs in none of these specimens. However, in another series of experiments similarly performed but in which the mother guinea pigs were later subjected to anoxemia or asphyxia, the fetuses executed respiratory movements and 9 out of 25 aspirated the thorotrast. Asphyxia at birth resulted in aspiration in three other animals.

These experiments lead us to believe that aspiration of amniotic fluid is not a normal function. Some investigators experimenting with the human being and the monkey have also confirmed these studies in the guinea pig. Other investigators using the human subject have observed aspiration of amniotic fluid, but there is no indication that physiologic conditions were maintained in the latter experiments.

In conclusion, let me emphasize the need of critical evaluation of experimental conditions in studies in physiology of the fetus. When this is done, one may well question whether all human fetuses exercise their respiratory mechanism in utero near term. Even those that do so need not be assumed to aspirate the fluid.

DR. JOSEPH L. BAER.—The soundness of Dr. Snyder's deductions was challenged by Dr. Windle. In this connection it occurred to me that it is common knowledge to all who are familiar with fetal heart tones in labor that there is a relationship between heart rate and uterine contractions. It is common knowledge that if we want a true evaluation of the fetal heart rate we instruct the supervisor or the intern not to listen immediately at the end of the contraction but to wait a moment or two. With the onset of a contraction, the fetal heart rate drops decidedly, then after the uterus relaxes, there is an equally rapid acceleration of the heart rate, somewhat above the normal rate for that fetus, and then it steps down to its normal rate until the next contraction occurs. Possibly that observation fits in with Dr. Windle's comments. Perhaps the fetal heart slows down because it gets adequate oxygenation from the blood of the placenta at the time

In view of the fact that we have been able to find post-partum hypertension only in the negress, we calculated the average pressure for normal white and colored patients during the prenatal and post-partum periods. One hundred case records of white and colored patients were studied in compiling the data recorded in Table II. The average prenatal pressure was also obtained for the patients in this series who showed the unexpected post-partum rise. Two facts are apparent. First, while prenatal pressures of normal white and colored patients are about the same, the normal colored patients tend to show a higher post-partum rise. Second, normal colored patients show a somewhat lower prenatal pressure than do those exhibiting the unexpected post-partum rise (Table II).

TABLE II. AVERAGE PRENATAL AND POST-PARTUM BLOOD PRESSURE WITH STANDARD DEVIATION

I. Normal patients	
a. Colored	
(a) Prenatal	
1. Systolic	109.48 \pm 7.39
2. Diastolic	66.55 \pm 6.7
(b) Post partum	
1. Systolic	120.8 \pm 11.1
2. Diastolic	77.38 \pm 7.9
b. White	
(a) Prenatal	
1. Systolic	110.1 \pm 6.5
2. Diastolic	69.0 \pm 5.1
(b) Post partum	
1. Systolic	114.15 \pm 8.1
2. Diastolic	73.9 \pm 7.3
II. Patients with post-partum hypertension	
(a) Prenatal	
1. Systolic	116.3 \pm 6.0
2. Diastolic	73.38 \pm 4.3

Tables III to X represent data from selected cases of post-partum hypertension designed to illustrate the salient features of this syndrome. Table III shows that the maximum pressure may occur as early as six weeks post partum, and Table IV reveals that the maximum rise may not occur until much later. This post-partum rise does return to normal and has been observed to remain there as indicated in Table V. While the duration of this hypertension is usually about ten weeks, it may last twenty-five weeks or more (Table VI). The case reported in Table VII supplies a number of interesting observations. The patient's pressure during pregnancy and labor was somewhat lower than it was a year previously. At no time during or after pregnancy was she aware of any illness despite the fact that she exhibited a marked unexpected post-partum rise lasting at least forty-two weeks. Observed in

UNEXPECTED POST-PARTUM HYPERTENSION

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FOR the purposes of this paper, "unexpected post-partum hypertension" is defined as an elevation of the blood pressure above physiologic limits as found by us at the routine six weeks' post-partum examination. Elevations above 140 systolic and 90 diastolic are considered abnormal. To eliminate all "toxemias of pregnancy" and cardiovascular renal disease, it is also required that the prenatal and immediate post-partum pressure be normal.

Elsewhere, one of us (H. M.)¹ has reported 23 cases of post-partum hypertension. Since that time, we have observed 28 additional cases which have confirmed our original observations and brought to light some new and interesting data. Our routine has been simple: Cases of post-partum hypertension were carefully studied in the obstetric clinic and then referred to various departments of the outpatient clinic for special study. In most instances medical examination was followed by ophthalmoscopic examination, x-ray, electrocardiogram, blood, urine, and kidney function studies.

The salient features of this condition may be noted upon reference to the tables of data. In Table I it may be noted that most of the patients are multiparas. They were for the most part observed during pregnancy long enough to obtain adequate control data on the blood pressure. The post-partum hypertension usually lasts six to seventeen weeks. The attainment of the maximum pressure may not occur until the sixteenth post-partum week, though usually the maximum is seen about the sixth post-partum week (Table I).

TABLE I

I. Age	18-20 2 cases					20-30 15 cases					30-40 11 cases	
II. Gravida	i	ii	iii	v	vi	vii	viii	ix	x	xi	xiii	
Cases	4	8	2	3	1	3	1	2	2	1	1	
III. Enrolled	First Trimester					Second Trimester					Third Trimester	
	5					19					4	
IV. Number of prenatal visits	3-5					5-10					over 10	
Cases	4					6					18	
V. Number of pregnancies with post-partum rise											40	
Unknown duration of post-partum rise											21	
Known duration of post-partum hypertension											19	
Six to seventeen weeks post partum											15	
Seventeen to twenty-two weeks post partum											2	
Forty-six weeks post partum											1	
Forty-nine weeks post partum											1	
VI. Maximum post-partum blood pressure												
Weeks post partum			6	7	8	8	10	11	16			
Cases			20	3	3	1	4	1	1			

TABLE VI

43574, aged 32, gravida x, second trimester, 5 prenatal visits	
Blood pressure during pregnancy	115-148
	70-84
Blood pressure six weeks post partum	170/105
Blood pressure seven weeks post partum	160/100
Twenty-four weeks post partum	154/94
Twenty-five weeks post partum	160/100
Forty-six weeks post partum	120/90
Seventy-five weeks post partum	120/90
Four months prior to pregnancy the blood pressure was 142/96.	
Laboratory and physical examinations negative.	

TABLE VII

87377, aged 32, gravida viii, second trimester, 19 prenatal visits	
Blood pressure during pregnancy	120-134
	68-84
Blood pressure during labor	108-118
	68-88
Blood pressure six weeks post partum	148/110
Nine weeks post partum	200/130
Twenty weeks post partum	220/120
Twenty-eight weeks post partum	160/100
Thirty-six weeks post partum	180/115
Thirty-eight weeks post partum	164/94
Forty-two weeks post partum	156/100
One year before the onset of pregnancy the blood pressure was 140-154/80-88.	
Blood picture, urinalysis, Wassermann, chest plate, and basal metabolism negative.	
Eye grounds, marked arteriosclerosis.	
Medical diagnosis: hypertensive vascular disease.	

TABLE VIII

110-492, aged 28, gravida v, first trimester, 12 prenatal visits (1934)	
Blood pressure during pregnancy	100-122
	60-78
Blood pressure six weeks post partum	168/120
Blood pressure eight weeks post partum	126/88
Twelve weeks post partum	120/90
Sixteen weeks post partum	124/92
(1936-37), aged 31, gravida vi, first trimester, 12 prenatal visits	
Blood pressure during pregnancy	100-118
	60-80
Blood pressure during labor	130/96
Blood pressure six weeks post partum	146/100
Seven weeks post partum	140/105
Thirteen weeks post partum	138/90
Twenty-six weeks post partum	136/94
Thirty-seven weeks post partum	136/96
Laboratory and physical examination negative.	

Certain facts not recorded in the tables are worthy of comment. Upon survey of the literature, it was found that "unexpected post-partum hypertension" has been recorded on only two occasions.^{1, 2} Stout found

TABLE III

152-491, aged 20, primipara, second trimester, 8 prenatal visits	
Blood pressure during pregnancy	112-120
	70-86
Blood pressure during labor	130-136
	70-80
Immediately post partum	135/85
Six weeks post partum	160/120
Twelve weeks post partum	150/105
Thirteen weeks post partum	130/85
Fifty-one weeks	118/88
Blood picture, chemistry, urinalysis, eyegrounds, chest plate, and physical examination all negative.	

TABLE IV

114-383, aged 29, gravida v, first trimester, 19 prenatal visits (1937)	
Blood pressure during pregnancy	108-124
	70-80
Blood pressure during labor	132/84
Blood pressure 6 weeks post partum	146/94
Blood pressure 10 weeks post partum	154/100
Blood pressure 11 weeks post partum	170/110
Blood pressure 12 weeks post partum	160/110
Blood pressure 13 weeks post partum	118/96
Blood pressure 14 weeks post partum	130/95
Blood pressure 15 weeks post partum	130/88
Blood pressure 16 weeks post partum	115/80
Blood pressure 18 weeks post partum	130/85
Blood pressure 20 weeks post partum	130/85
Blood pressure 79 weeks post partum	122/80
Physical examination and laboratory test entirely negative.	

TABLE V

14942, aged 38, gravida ii, second trimester, 13 prenatal visits	
Blood pressure during pregnancy	90-114
	60-72
Blood pressure six weeks post partum	192/110
Seven weeks post partum	190/110
Thirteen weeks post partum	152/110
Fourteen weeks post partum	122/80
One hundred twenty-four weeks post partum	116/80
One hundred thirty-four weeks post partum	138/80
One hundred thirty-six weeks post partum	130/80
Wassermann, Fishberg, urinalysis, and physical examination negative.	

the post-partum period, a diagnosis of arteriosclerosis of the retinal vessels and hypertensive vascular disease was made.

Table VIII illustrates that post-partum hypertension can and does recur with succeeding pregnancies and that a repetition of the syndromes may be less severe than the preceding one. This speaks for a functional disorder rather than an organic disease. As a matter of fact, the post-partum rise may be entirely absent in subsequent pregnancies as shown in Table IX. In Table X it can be seen that the unexpected rise occurs in 3 successive pregnancies after a normal post-partum blood pressure in the first pregnancy.

of the syndrome was significant. In no other case was a diagnosis suggested. The possibility of confusing "unexpected post-partum hypertension" and hypertensive vascular disease (essential hypertension) is a real one and the guarded prognosis of the latter given to the post-partum patient is entirely unwarranted.

We have as yet failed to observe congestive heart failure in any case of post-partum hypertension. The possible relationship of this syndrome to the curious post-partum congestive heart failure reported³⁻⁵ is at present quite obscure.

SUMMARY

1. "Unexpected post-partum hypertension," coined term, is an idiopathic syndrome, relatively unstudied, and found by us only in the colored race.

2. The findings in 51 cases are summarized in this report.

3. Most of the patients are multiparas.

4. Practically all of the patients were observed during the prenatal period for an adequate time period to allow for evaluation of the post-partum blood pressure.

5. The duration of the post-partum rise is about six to seventeen weeks. It is self-limited.

6. The maximum pressure while usually observed six weeks' post partum may be as late as 16 weeks post partum.

7. The average normal colored patient shows a slightly higher post-partum pressure than does the average normal white patient. The average normal colored patient shows a lower prenatal pressure than does the colored patient who develops "unexpected post-partum hypertension."

8. The syndrome may or may not be present at subsequent pregnancies and if so, may be more or less severe than the previous occurrence.

9. No relationship of this syndrome to post-partum heart failure (idiopathic) has been apparent.

10. No etiologic factor is evident; there is some suggestion that it is purely functional.

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TABLE IX

90419 The blood pressure during three pregnancies from 1928 to 1933 never exceeded 128/80, an average of 100 to 116.	
1935, aged 27, gravida iv, second trimester, 14 prenatal visits	
Blood pressure during pregnancy	112-136
	<u>70-84</u>
Blood pressure six weeks post partum	180/110
Blood pressure ten weeks post partum	172/114
Blood pressure fourteen weeks post partum	192/112
Blood pressure eighteen weeks post partum	180/120
1937, aged 29, gravida v, second trimester, 14 prenatal visits	
Blood pressure during pregnancy	110-132
	<u>70-86</u>
Blood pressure six weeks post partum	120/78
Blood pressure ten weeks post partum	120/86
Blood pressure one year post partum	126/88

TABLE X

136-490, aged 28, gravida i, third trimester, 5 prenatal visits (1934-35)	
Blood pressure during pregnancy	122-140
	<u>70-80</u>
Blood pressure during labor	124-138
	<u>80-94</u>
Blood pressure six weeks post partum	120/72
(1936) Aged 29, gravida ii, second trimester, 15 prenatal visits	
Blood pressure during pregnancy	108-130
	<u>60-84</u>
Blood pressure during labor	122-128
	<u>70-84</u>
Blood pressure six weeks post partum	148/98
Blood pressure seven weeks post partum	144/96
Blood pressure eleven weeks post partum	150/80
Laboratory and physical examination negative.	
(1937-38) Aged 31, gravida iii, first trimester, 22 prenatal visits	
Blood pressure during pregnancy	112-134
	<u>58-78</u>
Blood pressure during labor	110-122
	<u>78-84</u>
Immediately post partum	126/80
Six weeks post partum	160/105
Ten weeks post partum	130/95
Laboratory and physical examinations negative.	
(1938-39) Aged 32 gravida iv, second trimester, 16 prenatal visits	
Blood pressure during pregnancy	112-140
	<u>60-80</u>
Blood pressure during labor	130-144
	<u>84-100</u>
Immediately post partum	126/80
Six weeks post partum	140/100
Laboratory and physical examinations negative.	

that it occurs in white as well as colored patients; we have found it only in colored patients.

When these patients were observed in the medical clinic, a diagnosis of hypertensive vascular disease seemed warranted in all instances, although only two patients in the entire series showed any vascular damage and that was limited to the eye grounds. The seeming self-limitation

TECHNIQUE OF THERAPY

The following articles are necessary for a treatment:

1. An apparatus capable of delivering a direct current of 15 to 20 milliamperes (Fig. 1).
2. A vaginal electrode consisting of an insulated metal rod terminating at one end in a small mobile crosspiece.
3. 20 c.c. of $\frac{1}{2}$ or 1 per cent mecholyl chloride and enough gauze for saturation.
4. An abdominal galvanic pad 6 by 8 inches.
5. A bivalve vaginal speculum, sponge stick, and sponges.

The procedure follows:

The pad is first soaked in warm tap water; if not wet enough, it may be difficult to raise the milliamperage. With the patient in the lithotomy position, the cervix is exposed and the vaginal vault wiped dry, so that the drug may make close contact. The gauze saturated with mecholyl chloride is then wrapped about the vaginal end of the electrode, held firmly against the vaginal vault with the crosspiece at right angles to the shaft, and the speculum carefully withdrawn. The

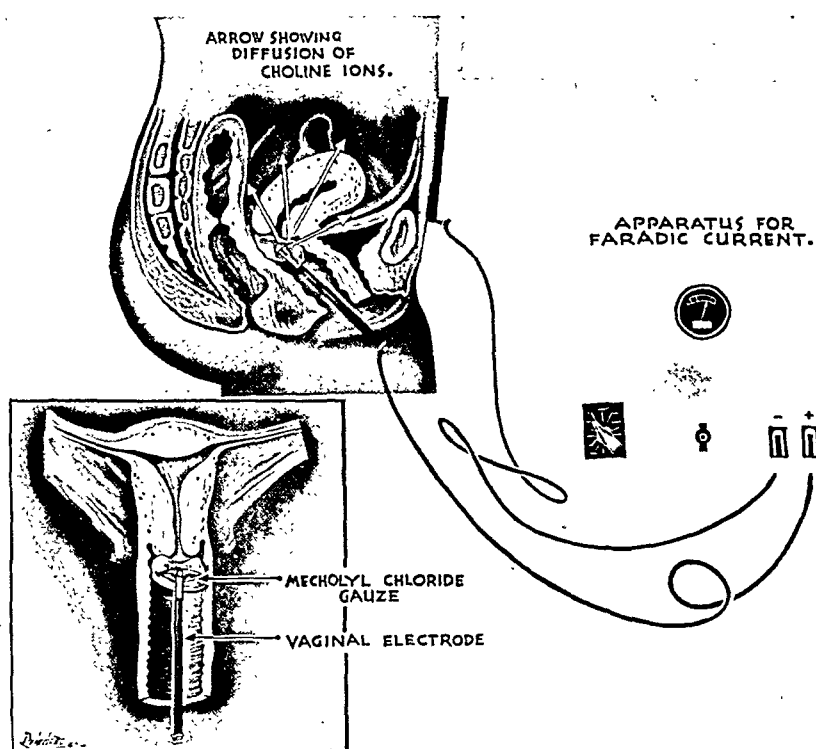


Fig. 1.

electrode is then attached to the positive pole, the current turned on, and increased slowly to 15 or 20 milliamperes. The patient generally experiences a slight local sensation of shock if the current is increased too quickly. The abdominal pad is held firmly against the skin by a binder or sandbags. A sensation of pricking, burning, or sticking, due to failure of the pad to make sufficient contact, may be eliminated by having the patient press it down with her hands. The treatment should last twenty minutes, when the current should be decreased slowly, or the patient may again experience slight local shocking.

Increase in the pulse rate, flushing, sweating, lacrimation, and salivation should be looked for, so as to be certain that absorption of sufficiently active solution of the drug is taking place. Treatments should be given every other day for two to four weeks, depending upon response to therapy.

STUDIES IN PELVIC IONTOPHORESIS*

I. IONTOPHORESIS IN THE TREATMENT OF PELVIC INFECTIONS WITH A REPORT OF 58 CASES

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PELVIC infections are very common. Approximately 500 cases a year in the wards at Kings County Hospital constitute our major problem. Radical operations are clearly contraindicated in young women and, in our experience, anything less is likely to be unsatisfactory. The clinical course of the infection depends, above all, upon its etiology and pathology. Mixed forms, largely due to gonorrhea and postabortive or puerperal infection, are common. In the majority of cases there have been frequent exacerbations. Actual resolution of large masses not infrequently occurs and symptoms tend to improve or subside with hospitalization. Improvement is so consistent as a matter of fact, that we believe that exacerbation follows re-infection, and that relief of symptoms is due to removal from the dangers of coitus, not bed rest alone. Operation has been performed for drainage of ovarian abscess, intraperitoneal abscess, whether abdominal or pelvic, and for relief of prolonged menorrhagia, severe dyspareunia, and disability of long standing. Our experience with conservative or nonoperative treatment has been discouraging. Foreign protein, repeated transfusions, and various forms of heat therapy have been unsatisfactory.

In August, 1940, we¹ reported our results with sulfanilamide in 74 cases of severe pelvic infection, concluding that this therapy should be used only in those acute cases in which the gonococcus or streptococcus was the infective agent. We observed no notable diminution in the size of pelvic masses, tuboovarian or otherwise. Cellulitic lesions did not respond at all. Sulfathiazole is now being given a trial.

Following the reports of Jacoby^{2, 3} on the rapid absorption of exudates by pelvic iontophoresis of acetyl-beta-methylcholine chloride (mecholyl chloride), we selected patients for this form of therapy. In subsequent papers we shall report upon the physiology of iontophoresis, and its use in fibroid tumors of the uterus with associated pelvic inflammation.

Iontophoresis is the act of driving positively or negatively charged ions into the tissues underlying the skin or mucous membranes by means of a galvanic or direct current. The intent with the use of mecholyl chloride is to produce local hyperemia,⁴ said to be more intense and more prolonged than that initiated by heat therapy. The local effect is clearly vasodilatation, probably of the capillary bed, with fall in blood pressure, increase in the pulse rate, salivation, lacrimation, flushing, and sweating. This systemic response follows oral or subcutaneous administration as well.

*Read at a meeting of the Brooklyn Gynecological Society, October 4, 1940.

PERSONAL OBSERVATIONS

During the past two and one-half years, 37 patients with tuboovarian and 21 patients with cellulitic infection were selected for treatment; 43 were from the Kings County Hospital and 15 from the service of Dr. Alfred C. Beck at the Long Island College Hospital.*

Diagnosis and the extent of the pathology were based principally on the pelvic findings of unilateral or bilateral tender inflammatory masses; in 12 cases these masses were so large as to be felt abdominally. In 21 cases there was evidence of previous severe infection, and in 11 cases a history of operative procedures including salpingectomy, colpotomy, intratubal injection of turpentine, and drainage of a Bartholin abscess. Pain and menstrual disturbances were common. In 15 cases abscess or pelvic peritonitis or both were present. In 13 cases of cellulitis, the exudate almost filled the pelvis, rising higher in 7 cases and to the iliac crest in 4. Three or more treatments with an average of 6 were given to 42 patients.

In the majority of cases, the patient had failed to respond to some form of therapy, and in 13 cases repeated blood transfusions and sulfanilamide therapy had been ineffective. In 27 cases, more than one week without clinical improvement had elapsed. This is a fair test, yet we realize that even a much longer period is open to question.

Occasionally, marked relief of pain, out of proportion to other evidence of clinical improvement, was noted. We have, however, based our opinion as to the value of therapy on objective response alone. Relief of pelvic pain was observed in 32 of the 42 patients who were treated adequately, and in 12 of the 16 patients receiving less than three treatments. One patient died of a postoperative cardiac complication one month after iontophoresis therapy had been finished. Decrease in size or disappearance of inflammatory masses or tenderness, normal levels of the leucocyte count and sedimentation time, and increased mobility of the pelvic viscera are excellent signs of improvement. In the case of tuboovarian disease, satisfactory change in the sedimentation time is good evidence of subsidence of infection. In this group of 37 patients, 24 received adequate treatment; in 14 of these, marked reduction in size of adnexal masses was observed.

In cellulitic infections the exudate is more readily observed. In 2 cases iontophoresis was given to patients thought to have deep parametrial abscesses in the hope of making incision and drainage easier. Resolution followed. When the exudate was small and of long standing, improvement as a rule was not remarkable.

Four cases have been selected to illustrate apparently good results.

CASE 1.—A. G., aged 39 years, para iv, was admitted on July 8, 1940, complaining of lower abdominal pain for thirteen days. Temperature was 103° F., sedimentation time twenty minutes for 18 mm., and the leucocyte count 12,950 with 87 per cent polymorphonuclears. The lower abdomen was very tender, and both adnexa were enlarged, cystic, and tender. After two weeks in bed, repeated blood transfusions, and full sulfanilamide therapy, the sedimentation time remained unchanged.

After 11 iontophoresis treatments, the sedimentation time became eighty-five minutes. At laparotomy on August 8, the left tube and ovary were found grossly normal, and the right tube and ovary moderately thickened and adherent to each other. Pathologic examination of the right tube and ovary showed minimal evidence of infection (Fig. 2).

CASE 2.—H. K., aged 18 years, was admitted on Jan. 15, 1938, with a history of pain in the right lower quadrant of the abdomen for three weeks. Temperature was 103° F., sedimentation time 25 minutes for 18 mm., and the leucocyte count 20,000 with 85 per cent polymorphonuclears. The lower abdomen was tender and spastic with peritoneal rebound pain. A diagnosis of pelvic peritonitis and cellulitis was made, and the patient received repeated blood transfusions and two courses

*We are indebted to Dr. Wm. A. Jewett, Dr. Harvey B. Matthews, and Dr. George W. Phelan for these cases.

2. Subjective improvement was generally marked, and often out of proportion to objective evidence of decrease of the infection.

3. The results of therapy in tuboovarian infections, while often good, were not sufficiently remarkable to warrant routine use of this method of treatment. It seems clear that we cannot hope for resolution of old inflammatory tuboovarian masses, since fibrosis and multilocular cysts are a prominent part of the pathology. It may, however, be given a trial in persistent tuboovarian infections, when operative treatment is not indicated and other methods of treatment have been ineffective.

4. The best response to iontophoresis was seen in cases of massive cellulitic infection of recent origin which had failed to yield to ordinary treatment. Pelvic iontophoresis is recommended for this type of infection.

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A SURVEY OF FOUR HUNDRED AND TWENTY-FIVE CASES OF TOXEMIA OF PREGNANCY

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THE selection of a title adequately and accurately describing the work herein presented was difficult. We fully realize that the term "toxemia of pregnancy" denoting a "diagnostic trash can," is an ineffectual cloak for ignorance, and in the light of most recent investigation, is in all probability a misnomer. All of these opinions have been recognized and previously stated by others investigating the problem.

We do not feel that this survey will contribute anything new toward clarification of this maze, but present the series with the hope that it will in some measure add to the data already existent.

For want of a better term, and because it describes a syndrome familiar to the clinician and research worker alike, we too make use of the designation "toxemia of pregnancy," in the belief that this terminology will soon become obsolete in medical literature.

This series covers a ten-year period in the Department of Obstetrics at the New York Infirmary for Women and Children. During this time there were 7,293 deliveries, with a maternal mortality rate of 0.18 per cent. Of these deliveries, 425 occurred in women on whom a diagnosis of "toxemia of pregnancy" was made, in which group there was a mortality of 0.4 per cent. All of the cases presented occurred in the latter half of pregnancy, excluding therefore, pernicious vomiting of pregnancy which is included by others in discussing the subject of toxemia as a whole.

readmitted with a large cellulitic exudate which extended to the crests of both ilia. Temperature reached 103° F. She was treated by bed rest and repeated blood transfusions for a month without appreciable improvement.

From April 3 to June 4, 9 iontophoresis treatments were given. The first treatment relieved the pain which had persisted for a few months, and by May 30, after 6 treatments, she felt entirely well. When discharged on June 19, only a small mass remained. On follow-up examination on Oct. 31, 1938, small bilateral mobile, nontender, tuboovarian masses were noted. One year later she was well, and no masses or exudates could be felt on pelvic examination (Fig. 4).

DISCUSSION

The common symptoms of systemic reaction were observed, yet all were not present in every case. In addition, dizziness, frontal headache, dryness of the mouth and throat, palpitation, trembling, chilly sensations and pain in the lower abdomen, and vagina were rarely observed. Though vasomotor collapse is said to occur, we have not seen it, yet one patient did experience tachycardia and marked difficulty in breathing which improved at once when treatment was discontinued. One galvanic burn of the skin, in the shape of multiple small superficial ulcers, was observed; it subsequently healed. These burns are probably caused by electrolytic changes, and not by generation of heat or sparking beneath the pad. They may be due, of course, to electrode metal touching the skin, insufficient thickness of the pad, or skin defects.⁵

In 4 cases treatment appeared to aggravate the lesion. Failure of subjective improvement generally indicates a poor prognosis for therapy, though we have seen increased activity of the infection followed by resolution. In 4 cases a slight rise in temperature during the twenty-four hours following treatment was noted.

On the basis of objective findings alone, we have classified our results in 42 patients who received adequate therapy, since it is our opinion that less than three treatments with iontophoresis is inadequate therapy.

Group I: Good Result. Those who improved on iontophoresis after failure of supportive therapy, blood transfusion, and chemotherapy, and those who showed striking improvement, though the control period had been short.

Group II: Doubtful result. When response had been good, but not more than might be expected on supportive therapy.

Group III: No effect. When the pelvic findings were essentially unchanged.

Group IV: Harmful result. When clinical evidence of exacerbation of infection followed therapy.

TABLE I. EVALUATION OF THE THERAPY

RESULT	TUBOOVARIAN INFECTIONS	CELLULITIC INFECTIONS		TOTAL
		MASSIVE	MODERATE	
Good	10	7	1	18
Doubtful	10	2	3	15
None	0	3	1	4
Harmful	4	0	1	5
Total	24	12	6	42

SUMMARY

1. Pelvic iontophoresis of a choline compound was given to 58 patients with subacute and chronic pelvic infection, all severe enough to warrant hospitalization; 37 were cases of tuboovarian infection and 21 were cases of cellulitis.

dures, and have taken into consideration the patient's past personal history, and have investigated the familial background. Wherever possible, especially during the past few years, we have included in our routine work-up an ophthalmologic consultation for opinion as to the findings in the fundus oculi.

MATERIAL

Our criteria for the division of cases into groups is outlined as shown in Table I.

Among our pre-eclampsias there are 116 cases which would in all probability be classified as "low reserve kidney" by Stander and his followers. In our hospital these patients are described as having pre-eclampsia of a mild degree.

In tabulating the groups, Table II will serve to illustrate the distribution of cases.

TABLE II

TYPE	PRIMIPARAS	MULTIPARAS	TOTAL
A. Pre-eclampsia	216	56	272
B. Eclampsia	13	3	16
C. Nephritis	41	69	110
D. Vascular	19	8	27

These findings coincide in the main with those published by other investigators with possibly one exception. We seem to have a higher incidence of chronic nephritis among our primiparous patients than is usually reported.

INCIDENCE

The age grouping in the series covers a wide range. It has usually been assumed that toxemia is an affliction of the young primipara, with the exception of the frequent occurrence of the nephritic type among older women, especially those who are multiparous. The ages of the patients presented in this survey range from 15 to 45. For simplicity the age incidence has been outlined graphically (Fig. 1).

MANAGEMENT AND THERAPY

The private cases totaled 70, leaving six times as many ward cases handled through the clinic and by the staff of the obstetrical department. The management of the private cases remained in the hands of the physician referring the case for hospitalization, but most of these were handled according to the departmental routine, and treatment, with very few exceptions, was essentially the same as that used in the service cases.

Most of the patients were treated according to the method now in use, which is described in detail later. There were, however, 62 patients admitted and delivered before any system of therapy could be instituted, and in these cases only the post-partum period was managed according to routine. In addition there were 38 cases occurring in the earlier years covered by this report that received a now out-dated mode of treatment. This method in the main comprised limitation of fluids,

CLASSIFICATION

Our system of classification is one approved and accepted by the American Committee on Maternal Welfare, and we consider it to be simple and inclusive. Our cases are therefore grouped as follows: (A) pre-eclampsia, (B) eclampsia, (C) chronic nephritis, (D) essential hypertension (vascular), and (E) unclassified.

Although there are some people who do not feel that accurate classification can be based on the occurrence of hypertension, urinary abnormalities, and other findings in use as diagnostic aids, nevertheless, for the want of more satisfactory resources, we have depended to a certain degree on all of these factors. In addition to the clinical picture presented by the patient, we have carried out routine laboratory proce-

TABLE I. CRITERIA FOR CLASSIFICATION OF VARIOUS FORMS OF TOXEMIA

	PRE-ECLAMPSIA	ECLAMPSIA	CHRONIC NEPHRITIS	VASCULAR
Age	Usually young	Usually young	Usually older	May be any
Parity	Usually primiparas	Usually primiparas	Usually multiparas	May be either
History	Normal	Normal	Chronic	Normal or abnormal
Symptoms	*Same as eclampsia without convulsions	Headache Edema Irritability Dizziness Visual disturbances Nausea Vomiting Epigastric pain Suppression of urine Jaundice (rare) Convulsions	Headache Edema Polyuria Dizziness Visual disturbances	*Headache Edema Epistaxis
Onset	Late	Late	Early	Early
Blood pressure	Elevated Drops early	Elevated Drops early Diastolic high	Elevated Remains high Diastolic low	Elevated Remains high Diastolic high
Urine Albumin Specific gravity Microscopic	1-2 plus Normal Usually negative	3-4 plus High May have red blood cells, casts, pus	1-4 plus Low and fixed Casts	*1-4 plus Varies *Casts
Blood Chemistry Urea nitrogen Uric acid Chlorides Proteins	Normal Normal (severe-elevated) Normal Normal	15-20 3.5-5 or more Increased Usually decreased	20-30 3.5-5 or more Increased Decreased	Little or no change
Urea clearance	Normal	Normal	Usually below 70%	Normal
Eye Grounds	Normal	Spasm of retinal vessels	Albuminuric retinitis	Arteriosclerosis

*May be variable or absent.

blood pressure, check of the gain in weight, and examination on the table. In the course of this examination the height of the fundus is measured, the heart examined, and the presence or absence of edema noted. In addition, each patient is questioned carefully to elicit any complaint. Specific questions are asked concerning gastrointestinal upsets, headache, visual disturbances, dizziness, undue irritability, and swelling of any part of the body. When a patient presents any finding which indicates that she presents a potential or actual toxemia, she is seen by the attending physician or resident and placed on the routine proper for her phase of the condition.

To clarify the terms "potential" and "actual" toxemia as recognized in our clinic, we refer to the history, both personal and familial, and consider in addition the general physical constitution as to endocrine type of the patient. In patients whose physical type or history would seem to predispose to some form of toxemia a designation of potential toxemia is made. This group is given explicit instruction as to diet, rest, sodium chloride intake, and fluid intake and output. In addition these patients are impressed with the importance of keeping clinic appointments and are followed by Social Service to insure regular visits. Wherever indicated basal metabolic rates are taken and thyroid administered if necessary.

Patients considered actual toxemias are those presenting recognized symptoms or signs in any degree. Symptoms presented by the cases in this series included the following: edema, nervous irritability, visual disturbances, headache, dizziness, epistaxis, gastric disturbances, jaundice, and convulsions. There were a few patients, three of whom proved to be true eclamptics, who denied complaint and who presented no premonitory signs whatever until the actual seizure. In all patients excessive weight gain, elevation of blood pressure, and albuminuria were considered of diagnostic import.

Edema was by far the most common and often the earliest manifestation. It is interesting to note that 196 patients complained of only a single symptom as outlined: edema, 168; headache, 13; dizziness, 4; gastric disturbance, 4; visual disturbance, 4; epistaxis, 1.

Of those patients with a completely symptom-free picture, 36 were in the pre-eclamptic group, 12 were chronic nephritics, 3 were eclamptics, and 5 were in the vascular group. Twelve of these patients have been followed since delivery and to date 5 show definite evidence of permanent cardiovascular renal damage.

Potential cases are seen frequently in the clinic and watched carefully for signs or symptoms which might appear and place them in the group of actual toxemias.

In the patients with early mild symptoms, the following constitutes our preliminary regime:

1. Addition of protein and carbohydrate to the diet.
2. Advice as to adequate rest.
3. Administration of magnesium sulfate in four dram doses to be taken once daily.
4. Limitation of the intake of sodium chloride to only the amount used in cooking.

hot packs, low protein diet, morphine in large doses, heavy catharsis, and in a few instances, venesection.

Due to the emphasis now being placed on registration early in pregnancy, and the awareness on the part of the laity of the importance of this, most of the cases delivered without benefit of ante-partum treatment likewise occurred in this early period.

Our present routine in the clinic is begun as early as the symptoms appear, and every physician working in the clinic is on the lookout for danger signs.

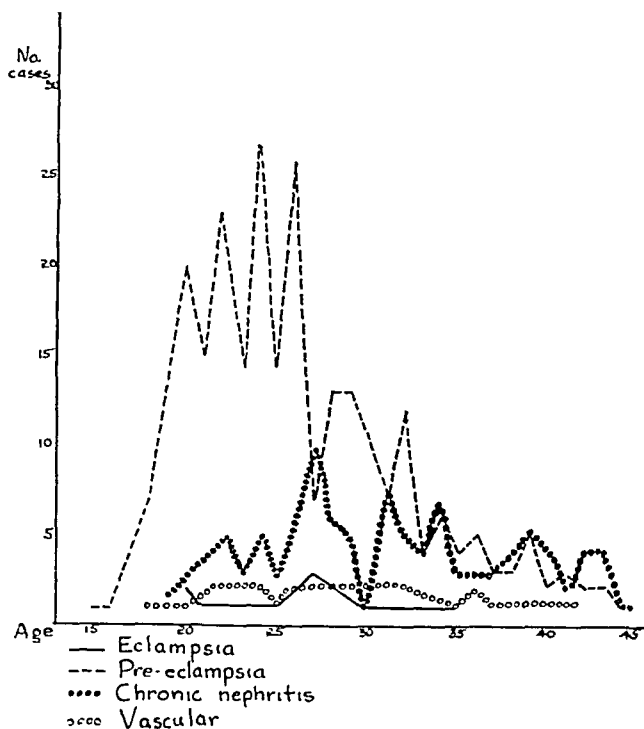


Fig. 1.—Graph showing incidence of various types of toxemia according to age.

Upon admission every obstetric patient receives a complete physical examination plus detailed investigation concerning the past personal and familial history, with special reference to hypertension and cardiovascular renal disease. Those patients in whom there is a history of previous cardiovascular renal disease, whose family shows a prominent history of the same, or in whom there is a history of previous pregnancy complicated by hypertension, renal disease, or toxemia as such, are designated for further study and close observation.

In investigating the personal histories of the patients included in this series, the following significant factors in their past histories were elicited: cardiac disease in 17, numerous infections in 36, spontaneous abortions in 46, pyelitis in 5, previous stillbirths in 7; convulsions, thyroid dysfunction, sterility, 2 each; syphilis, tuberculosis, diabetes, 1 each.

In any patient showing clinical signs of potential or actual toxemia, special attention and immediate action is our rule. Every clinic visit during the prenatal period includes a urinalysis, determination of

plain ether in oil in the milder cases. Gas-oxygen or drop ether, the former generally considered more desirable, is administered with pains during the stage of expulsion. Immediately following delivery of the placenta, the patient is again given morphine if necessary.

When convulsions occurred prior to delivery, all concern was naturally for the mother. In the cases occurring earlier in the series presented, ether was administered during the seizure and morphine was immediately given. These procedures were followed as soon as practical by intravenous administration of glucose and magnesium sulfate. The tendency at the present time is to give oxygen rather than ether and to omit morphine if possible because of the additional cerebral edema produced by the drug. Rest in a quiet location with constant attendance is still the rule.

In this series, there was a total of 16 convulsive cases distributed as follows: 3 ante partum, 6 intrapartum, and 7 post partum. In one case in which convulsions occurred five days post partum in a recurrent toxemia, oxygen through a nasal catheter produced such dramatic results and so much comfort was experienced by the patient that its use deserves special mention.

Regular blood pressure readings are taken on all post-partum cases and recorded twice daily. These patients are watched carefully for persistence, recurrence, or aggravation of signs and symptoms of toxemia. Blood chemistries are repeated as often as necessary and the routine continued as long as there are indications of active disease. All patients with toxemias are instructed on discharge to report both to the post-partum and medical clinics.

The use of phenobarbital is discontinued as soon as the patient shows definite lowering of blood pressure. In the vascular and nephritic types where there is frequently no fall in blood pressure, it is discontinued after three or four days. This has been done because of the depression often found with long-continued administration of the barbiturates.

The number of cases induced was 42 (9 per cent). Most of the patients admitted were able to return to their homes after treatment to be readmitted in spontaneous labor. Others went into labor while under treatment in the hospital.

Reports on the method of delivery in many hospitals show a high incidence of operative delivery. Of our 425 cases, 321 delivered spontaneously, leaving 24 per cent assisted deliveries. The methods of operative delivery included the following: Cesarean section, 21; low and midforceps, 66; breech extractions, 8; version and extraction, 8. Seventeen of the cesarean sections were performed for reasons other than the toxemia itself, including cephalopelvic disproportion, placenta previa, and premature separation of the placenta. Statistics in other hospitals show a larger percentage of operative delivery to be found among patients handled by private physicians. This does not seem so apparent in our group, with 3 per cent incidence among private deliveries and 2.3 per cent among the service cases.

These patients are instructed to report to the clinic after two weeks of this routine at home with warning to return earlier if necessary. If such a case is seen in the clinic after her two-week interval and shows no abatement of symptoms, or shows an aggravation of the condition, she is placed on a more rigid regime to be carried out at home if possible. Lack of space, a busy service, and in many cases the patient's home conditions prohibit routine hospital admission, although this would undoubtedly be the desirable procedure. The course followed under these circumstances involves cooperation with the local Visiting Nurse Service. The patient is sent home for absolute bed rest, and the visiting nurse requested to make frequent home visits. At these visits the patient is questioned as to complaints, blood pressure reading is taken, and urine examined for albumin. The nurse in turn reports to our clinic. In addition the following instructions are given:

1. Dietary restrictions and additions are reviewed.
2. Sodium chloride is eliminated entirely and potassium chloride substituted for palatability.
3. Phenobarbital is prescribed in 0.5 gr. doses three times daily.
4. Magnesium sulfate is continued in the same amount.
5. Calcium lactate is given in 10 gr. doses three times daily.
6. Absolute bed rest is stressed as imperative.

Vitamin B and iron are given routinely to all prenatal cases.

Patients so managed are told to report in one week to the clinic and in many cases improvement is noted. However, if there is no improvement, or if the case shows progression, hospital admission is then considered imperative.

The routine on the ward is essentially the same as that outlined for clinic management. In addition, intravenous glucose or glucose and magnesium sulfate as formulated by McNeil is given. In the hospital adequate supervision is the most valuable added factor.

In the past few years patients who had persistent appreciable amounts of pus in the urine, or who showed other signs or symptoms of pyelitis, were cystoscoped and wherever possible retention catheters were inserted to facilitate drainage. Nine such procedures were done in this group.

Many of the patients in this series remained from one to two weeks in the hospital and showed sufficient improvement to warrant discharge before delivery. These were followed satisfactorily in the clinic until term. However, cases near or at term on admission for treatment were usually considered as fit subjects for induction as soon as their condition made this possible. Medical induction, or medical induction followed by artificial rupture of the membranes, with or without the introduction of a Voorhees' bag, was the method of choice. A few patients were subjected to cesarean section purely because of the fulminating state of the toxemia.

During labor all toxemias are watched with particular care, and blood pressure determinations are taken at intervals of one to two hours. Adequate sedation is given, consisting usually of morphine in one-sixth grain doses with atropine in doses of 1/150 grain. This is supplemented toward the end of the first stage by rectal instillation of

cardiac consultation revealed no abnormality of the heart. At this time she had gained a great deal of weight and magnesium sulfate was given by mouth. There was apparent improvement until the ninth month.

Early in the ninth month the patient was admitted to the hospital with ruptured membranes and no pains. At this time the blood pressure was 140/92 with slight pitting edema of the ankles. The urine showed four-plus albumin and no pus. Labor was initiated by medical induction, and after thirty-three hours she was finally delivered by midforceps operation of a living baby, weighing 8 pounds. Her postpartum period was uneventful and blood pressure on discharge was 126/80.

In spite of contraceptive advice, this patient returned nine months later in the fourth month of her third pregnancy at which time her blood pressure was 114/62. From the middle of this pregnancy, there was an excessive gain in weight. During the eighth month urinalysis revealed three-plus albumin, and there was evidence of hydramnios with edema of the abdominal wall. The blood pressure had risen to 134/90, and she complained of dizziness and blurring of vision. She was admitted to the hospital.

In addition to the ward routine the patient had cystoscopic examination. The membranes ruptured spontaneously, and after a labor lasting sixteen hours she was again delivered by midforceps under gas oxygen anesthesia of a 13-pound stillborn infant. During labor the blood pressure varied between 190/110 and 120/80. Examination of the fundus oculi showed only spasm of the retinal vessels. The condition of the patient following delivery was poor, and in spite of supportive treatment death occurred ten hours later. Blood culture before death was positive for *B. coli*.

Autopsy findings revealed advanced bilateral acute pyelonephritis with hemorrhagic cystitis in addition to septicemia, early bronchopneumonia, and congestion of liver and spleen as well as generalized anasarca.

Two patients in this series died later of causes dependent upon and associated with previous toxemia. These are presented in detail.

CASE 3.—G. W., white, married, primipara, 34 years of age, was first seen in the clinic in the eighth month of pregnancy, weighing 181 pounds. On clinic admission physical examination was negative. Laboratory findings were normal and blood pressure was 118/72. Her condition was considered normal until the time of hospital admission.

On admission in the first stage of labor the blood pressure was 154/110. Urinalysis showed some pus and a trace of albumin. The blood chemistry showed urea nitrogen of 14 mg. and uric acid of 2.4 mg. At this time a soft systolic murmur was heard at the apex. Labor was extremely irregular, with intervals of complete cessation of pains. After sixty-two hours of ineffectual labor, manual dilatation of the cervix and delivery by midforceps was carried out, and a living baby obtained. The blood pressure after delivery was 134/95 and the urine showed a moderate amount of albumin. Dilution and concentration tests showed poor concentration. The puerperium was clinically normal.

Three years later this patient was admitted to the surgical department with the diagnosis of acute appendicitis. The blood pressure at this time was 116/66, urine showed a trace of albumin and a few casts. The urea nitrogen was 16.8 mg. and uric acid 2.5 mg. Her interval history was negative.

After appendectomy, the patient became semicomatose, and thirty-six hours after operation a slight asymmetry of the face was apparent, with inequality of the pupils, blurred speech, and flaccidity of the left upper extremity. The patient died forty-eight hours after operation.

Autopsy revealed thrombosis of the right middle cerebral artery, with softening of the right cerebral hemisphere, general cerebral arteriosclerosis, and generalized arteriosclerosis. There was also old rheumatic mitral valvulitis and cardiac hypertrophy (Fig. 2).

CASE 4.—V. C., white, primipara, married, 21 years of age, was first seen in the clinic in the fourth month of her pregnancy. Her past history was negative, but

COMPLICATIONS

Among the complications encountered were the following: pyelitis, 9 cases; premature separation of the placenta, 5; placenta previa, 2; post-partum shock and post-partum psychosis, 1 each.

Work has been done recently in an attempt to correlate the existence or history of pyelitis with toxemias of pregnancy. While a great many of our patients had small amounts of pus in casual urine specimens, there were only 9 cases presenting a true pyelitis during the course of the toxemia. Five patients had a history previous to the toxic state. In the follow-up of 109 toxic cases, 3 patients had pyelitis during a subsequent pregnancy. Two of these patients had recurrent toxemia of mild degree, complicated by the pyelitis, and one was a patient with recurrent toxemia, terminating in death from pyelonephritis.

MORTALITY

With the recent increased interest in maternal and infant mortality, it is pertinent to discuss our results and to correlate wherever possible the influence of induction and operative delivery with these results. There were 2 immediate maternal deaths in the series, giving a mortality rate of 0.04 per cent. One of these patients was delivered by cesarean section and the other delivered spontaneously. These deaths are presented in detail.

CASE 1.—M. B., white primipara, unmarried, 38 years of age, was seen for the first time as an emergency on the day of admission. At this time she was seven months pregnant. She had been treated at home by a physician for "yellow jaundice" of three days' duration, at which time she was told that her blood pressure was high and that there was albumin in the urine. Her past history was significant in that she had suffered recurrent respiratory infections, and two years previously had had a cerebral accident with hemiplegia on the right side.

On admission the blood pressure was 205/110. The skin was dry and yellow, and there was marked pitting edema of both legs. The laboratory findings revealed blood urea nitrogen to be 53 mg. The urine showed four-plus albumin, with many hyalin and granular casts.

The patient was placed on the old routine of liquid diet, hot packs, and colonic irrigations. Eight hours after admission she complained of pains in the neck and severe occipital and frontal headache. The following day the patient's appearance was poor, and there was some vaginal bleeding accompanied by uterine contractions and pain. A diagnosis of premature separation of the placenta was made and classical cesarean section was performed under ethylene anesthesia. The infant was stillborn and weighed 3 pounds and 11 ounces. During the operation, the blood pressure fell from 226/140 to 150/110.

The immediate postoperative condition was fair. Twenty-four hours after operation the patient complained of diminution of vision and thirty-six hours after operation she became stuporous. The blood pressure at this time was 186/124. Forty-eight hours after operation the patient died.

Autopsy findings consisted of hemorrhagic hepatitis of the eclamptic type and extensive tubular degeneration of the kidneys. Permission for examination of the head was not obtained.

CASE 2.—A. P., white, married, primipara, 24 years of age, was first seen in the third month of pregnancy, symptomless except for occasional nocturia. Past history revealed one spontaneous abortion ten months previous to clinic admission. At the time of admission her weight was 168 pounds, height 5 feet 1 inch. Her blood pressure was 120/70.

In the fourth month of pregnancy, she complained of ankle edema and dyspnea, although there was no change in the blood pressure. Urinalysis was negative and

per cent. The incidence of stillbirths in patients delivered operatively was 0.29 per cent and the neonatal rate was 0.19 per cent. These are corrected readings and do not include macerated fetuses.

Among 21 patients induced before 38 weeks, 21 living babies were obtained. Of these babies, 2 died in the neonatal period, 1 from prematurity and 1 from congenital deformities constituting a monstrosity. In addition, there was 1 macerated stillbirth in a set of twins. Seventeen of the stillbirths occurred in pre-eclamptic mothers, 1 in a true eclamptic, and there were 2 each in chronic nephritic and vascular types. Seven of the neonatal deaths occurred in babies delivered of pre-eclamptic patients, 2 from eclamptic patients, and 6 from nephritic and vascular forms of toxemia.

Among the causes of stillbirth other than toxemia were the following: prematurity and tentorial tears, 2 each; impacted shoulders, congenital edema, placenta previa, premature separation of the placenta, 1 each. Among the causes of neonatal death other than toxemia were: prematurity, 8; monstrosity, 3; congenital cardiac anomalies, 2; and neurocytoma, 1.

One hundred and six examinations of the fundus oculi were done. Of these, 58 showed fundi indicating changes in the vascular system. Our attempts to use our findings as diagnostic aids and prognostic signposts were somewhat disappointing as borne out by the information obtained in following our cases. Seventeen patients in whom positive eye findings were noted during the toxemia have remained so, while one who was positive at the time of her toxic pregnancy has since become negative. Of 15 patients with negative findings during the original onslaught of the disease, 13 on subsequent examination showed vascular changes.

FOLLOW-UP

In following our patients, we found recurrence to be much more frequent than has been generally reported. Many women showed evidence of permanent damage to the cardiovascular renal network, although a diagnosis of mild toxemia only had been made at the time of the admission to the obstetrical department. These follow-ups have covered a period of from one to seven years and total 109 cases. In the entire series 33 patients were actually recurrent toxemias, having originally come to us with the history of previous renal disease or true toxemia in a previous pregnancy. In addition, 71 patients later showed demonstrable evidence of damage as a result of their one toxic pregnancy. This statement is made on the basis of results obtained from blood chemistry examination, urinalysis, eye ground changes, and physical examination.

Of those patients returning with subsequent pregnancy, there were 28 in whom recurrence of the toxemia was evident, and only 8 with no demonstrable signs of recurrence. All these patients received careful supervision and were given all known prophylactic measures to prevent a return of the condition.

SUMMARY

We have presented a series of cases, numbering 425, termed loosely and possibly incorrectly "toxemia of pregnancy." No attempt is made to discuss the etiology. The classification used is standard.

Our methods of management, past and present, are outlined, admittedly conservative, from the earliest prenatal period to the final stage of delivery and puerperium.

Complications occurring in the mother and infant are presented and discussed; mortality statistics for both are given. From our follow-up,

there had been occasional swelling of the feet during her pregnancy. On her first visit the blood pressure was 116/70. She was referred to the dental clinic for treatment of marked dental caries.

Two weeks later urinalysis showed two-plus albumin; the blood pressure was 120/78; she had gained 6 pounds. At this time she complained of moderate ankle edema and nausea. She was admitted to the hospital whereupon her urine showed four-plus albumin, many pus cells and hyalin casts. Her hemoglobin was 55 per cent Sahli; blood urea nitrogen, 37.9 mg.; uric acid, 4.8 mg. In addition to the current routine, the patient was cystoscoped and a retention catheter inserted on the left side; the right ureteral orifice could not be identified. Urine culture showed the presence of *B. coli*. The eye grounds were found to be negative. Transfusion a few days later was followed by severe reaction. Sulfanilamide therapy was instituted.

Twelve days after admission labor intervened with the delivery of a five months' stillborn fetus. Following delivery, her temperature rose to 102° F. for two days and the blood pressure was 116/100. Ten days after delivery blood urea nitrogen was 88 mg. and uric acid 6.7 mg. The patient refused to remain in the hospital any longer and signed out under protest.

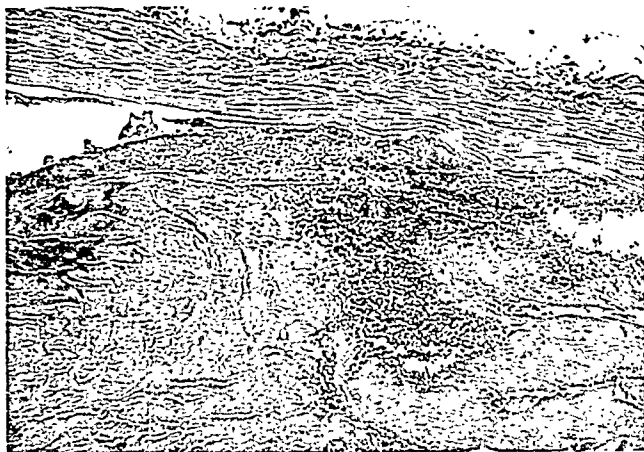


Fig. 2.—Case 3. Photomicrograph showing thrombosis in right middle cerebral artery.

Five months later she was admitted to the medical service with edema of the lower extremities. At this time she showed a clinical picture typical of chronic nephritis. After treatment she improved and was discharged from the hospital and never seen again. Reports have come to us recently that the patient died during an episode similar to that above approximately two years after delivery.

Fetal mortality is always reported as being high in the toxemias of pregnancy, especially in the eclamptic group. The London Committee reports a fetal mortality of 34.8 per cent in eclampsia, and Stander reports mortality figures of 30 per cent in the same group. Tillman and Watson found the highest figures occurring among the nephritic types where the mortality was 69 per cent. Cruikshank, Hewitt, and Couper found the neonatal mortality rate in eclampsia to be 17 per cent for mature infants and 54 per cent for premature infants. In our series there were 39 stillbirths for the entire group, an incidence of 9.6 per cent. Eighteen of these cases were macerated, and 5 were due to causes other than the toxemia. There were 15 neonatal deaths, an incidence of 3.5 per cent.

Among the 42 induced cases there were 2 stillbirths and 2 neonatal deaths. Of those patients delivered by operative methods, there were 14 stillbirths and 7 neonatal deaths. This leaves us with the remainder, numbering 23 stillbirths and 9 neonatal deaths, which occurred in spontaneously delivered patients in whom labor was initiated without interference. The stillbirth incidence in spontaneously delivered patients was 0.4 per cent and the incidence of neonatal mortality was 0.19

tions and fetal anomalies may play a part in the failure of a fetus to present correctly and must constantly be borne in mind when encountering the fetus which lies abnormally in the uterus. An excessive amount of mobility of the fetus making for variations from the normal cephalic presentation is often associated with multiple pregnancies, multiparity with its relaxed uterus and abdominal wall, premature labor or polyhydramnios. Not infrequently several causes may be associated with the failure of a fetus to present correctly: A word must be said about pure accident as a cause of abnormal presentations. The rupture of the amniotic sac at a time when the fetus lies in an unusual position will sometimes cause a shoulder presentation associated not infrequently with the prolapse of an extremity or umbilical cord.

The so-called oblique presentation often corrects itself early in labor and spontaneously becomes converted into a vertex or a breech presentation. The true transverse presentation may rarely terminate spontaneously if the child is very small or macerated. The child is almost always stillborn. This delivery by spontaneous evolution is too rare to be relied upon except in the instances cited above.

De Lee states that version, not expectancy, is the treatment of transverse presentations. Posture, external version before the onset of pains or early in labor, the use of a properly applied binder, or the application of a Willett clamp to the fetal scalp following external version are all useful procedures if intelligently employed in indicated situations. Under proper circumstances internal podalic version and breech extraction is the procedure of choice. The dilatation of the cervix and the amount of amniotic fluid are among the important factors to be considered.

The neglected transverse presentation presents an entirely different problem from the case which is correctly handled throughout. The danger of serious fetal and maternal complications in the former, not

TABLE I. DISTRIBUTION OF CASES ACCORDING TO PARITY, AGE OF MOTHER, DURATION OF PREGNANCY, AND TYPE OF PELVIS

FINDINGS	NUMBER			PERCENTAGE DISTRIBUTION		
	TOTAL	WHITE	COLORED	TOTAL	WHITE	COLORED
Parity:						
Gravida i	18	10	8	11.9	12.2	11.6
Gravida ii	26	14	12	17.2	17.1	17.4
Gravida iii to v	55	32	23	36.4	39.2	33.3
Gravida vi or more	52	26	26	34.5	31.5	37.7
Age Distribution:						
Below 20 years	11	5	6	7.3	6.1	8.7
20-31 years	78	44	34	51.7	53.7	49.3
32-35 years	33	13	20	21.9	15.9	29.0
36 years or more	29	20	9	19.1	24.3	13.0
Duration of Pregnancy:						
Less than 28 weeks	5	3	2	3.3	3.7	2.9
28-32 weeks	10	6	4	6.6	7.3	5.8
33-36 weeks	25	13	12	16.6	15.9	17.4
37-39 weeks	16	10	6	10.6	12.2	8.7
40 weeks	95	50	45	62.9	60.9	65.2
Pelvis:						
Normal	144	80	64	95.4	97.6	92.8
Contracted	7	2	5	4.6	2.4	7.2

we have felt that recurrence is more frequent than formerly thought. It is to be stressed that damage to the cardiovascular renal system is often of far-reaching consequence, even in supposedly mild cases of toxemia of pregnancy.

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TRANSVERSE PRESENTATIONS*

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THE development of obstetrics as an art has always been intimately blended with the condition of a people and the progress of their civilization. A certain perfection was attained even by primitive peoples, but quite strangely no real progress was made from the time of Hippocrates in Greece and the Ayur Veda in India until Paré and Vesalius laid the foundation of modern scientific obstetrics in the middle of the sixteenth century. Paré rediscovered podalic version in this period when empiricism gave way to scientific research with the study of anatomy and physiology and the acceptance of obstetrics as one of the branches of medical science. The use of the destructive operation as the only solution to a difficult labor was soon replaced by attempts to save the life of the child by version or forceps, and as a result the transverse and oblique presentation of the child became less formidable. More accurate knowledge of the pelvis, the uterus and the forces concerned in the expulsion of the fetus allowed a more scientific approach to the proper handling of abnormal presentations.

Many causative factors enter into the determination of the manner in which the fetus lies in utero. The occurrence of a transverse presentation with the long axis of the child crossing the long axis of the mother, usually obliquely, but occasionally at right angles, is fortunately not too common. This type of abnormal presentation occurs about once in every 200 to 250 cases. Factors preventing engagement of the fetal head in the pelvis and conditions allowing unusual mobility on the part of the fetus are perhaps responsible for the majority of instances of this error of polarity. Disproportion between the pelvic inlet and the fetal head must be immediately looked for, whether due to contraction of the bony pelvis or increased cephalic dimensions. This is true particularly in primiparas, but must also not be overlooked in the patient who has previously borne children normally. Obstructive pelvic tumors and low implanted placentas are occasionally encountered as the cause of unusual presentations. Uterine malforma-

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fetuses. There were several instances in which the Willett clamp was applied to the fetal scalp with most satisfactory results. Before the value of hysterostotomy was appreciated as it is today, severe cervical laceration with its resulting hemorrhage was far too frequently encountered, but in recent years prophylactic incision of the cervix in properly selected cases is a well worth-while procedure. In our series severe cervical tears occurred 11 times, and actual rupture of the uterus 4 times. These latter will be considered in more detail later on.

One of the most important considerations in any discussion of pathologic complications of pregnancy is the maternal and fetal morbidity and mortality. In this series 42 of the patients showed an elevation of temperature of 100.4° F. on two or more occasions following delivery, excluding the first twenty-four hours post partum, giving us an uncorrected morbidity rate of 27.8 per cent. Four of the mothers died, a maternal mortality of 2.6 per cent. There were 114 full-term infants, 35 of which were stillborn, a percentage of 30.7. Of the 37 premature fetuses, 19, or 51.4 per cent, were stillborn. Of the total number of liveborn, 13, or 13.4 per cent, died within ten days of birth. Excluding the deaths among premature infants from this group, the infant mortality rate for the first ten days was 6.1 per cent.

TABLE II. DISTRIBUTION OF CASES ACCORDING TO DURATION OF LABOR AND EFFECT ON CHILD

DURATION OF LABOR AT TIME OF DELIVERY	NUMBER			PERCENTAGE DISTRIBUTION			RESULT OF DELIVERY			
							NUMBER		RATE PER 100 CASES	
	TOTAL	WHITE	COL- ORED	TOTAL	WHITE	COL- ORED	STILL- BORN	LIVE- BORN	STILL- BORN	LIVE- BORN
Not in labor or less than 6 hours	41	26	15	27.2	31.7	21.7	7	34	17.1	82.9
6-11 hours	40	25	15	26.5	30.5	21.7	16	24	40.0	60.0
12-23 hours	33	16	17	21.9	19.5	24.6	11	22	33.3	66.7
24 hours or more	37	15	22	24.4	18.3	32.0	20	17	54.0	46.0
All cases	151	82	69	100.0	100.0	100.0	54	97	35.7	64.3

A most interesting observation is the relationship between the duration of labor at the time of delivery and the infant mortality. Of the entire series, 41 patients, or 27.2 per cent, were not in labor or were in labor less than six hours; 26.5 per cent were in labor six to twelve hours; 21.9 per cent in labor thirteen to twenty-four hours; and 24.4 per cent for twenty-five hours or longer. The prolonged labors were far more common among the colored patients showing definite evidence of less proper care. The effects of this prolongation of labor on the number of stillbirths is borne out by a percentage of 17.1 stillborn fetuses among the group of patients not in labor or in labor less than six hours, as compared to a gradually higher figure as the duration of labor increased. In the group of patients in labor twenty-five hours or more, the percentage of stillborn children was 54.

The relationship between the type of delivery and the condition of the child at birth is also important. In 17 patients the shoulder presentation was corrected by external version, and in this group of patients, only 5.9 per cent of the babies were stillborn. On the other hand, in 87 cases in which internal version and breech extraction was the method of delivery, 32.2 per cent of the babies were stillborn. This clearly demonstrates the danger of this procedure, particularly since 2 of the 4 maternal deaths and 3 of the 4 ruptured uteri, in the entire series, occurred in patients on whom version and extraction was done.

A word or so concerning the instances in which a rupture of the uterus or a maternal death occurred should be of interest.

infrequently associated with a ruptured uterus or a destructive operation on the child, is in marked contrast to the satisfactory results for all concerned if good obstetric art is employed.

Realizing the dangers associated with this abnormality in the polarity of the fetus in utero, it was decided to review the transverse presentations occurring at the University Hospital in Baltimore from June 1, 1920, to Dec. 31, 1939 (Table I).

STATISTICS

During this period of time there were admitted to the hospital 151 cases of shoulder presentation. Eighty-two of these occurred among white patients, and 69 among colored, 54.3 and 45.7 per cent, respectively. One hundred and thirty-three of the 151 patients were multiparas, and 70 per cent of these were gravida iii or more. In fact, more than a third of the patients were gravida vi or more. Thus, multiparity as a well-known factor is borne out in our series.

In so far as age is concerned, the age group of 20 to 31 years predominated and contained over half of the cases. Only 11 of the patients were below 20 years of age and almost one-fifth of the series were 36 years or older. The youngest age group was about evenly divided between white and colored but the oldest group of 36 years or more was almost twice as large in the white group as in the colored.

Multiple pregnancy occurred 10 times or an incidence of 1 in 15 in contrast to the frequency of about 1 in 80 normally encountered for twins. The duration of pregnancy at the time of delivery shows that 37.1 per cent of the fetuses were not at term. This presence of an undersized fetus in more than one-third of the cases combined with a preponderance of multiparas bears evidence of at least some of the factors concerned in the cause of shoulder presentations.

Contraction of the pelvis was encountered in an extremely small number of instances, only 7 patients showing considerable pelvic contraction, a percentage of only 4.6. Five of these 7 were in colored patients. Other series reported show a larger figure than this, and the importance of pelvic abnormality must not be minimized.

The length of time which the membranes have been ruptured has always been felt to be a most important consideration in determining the method of handling a particular case. This event, allowing the escape of amniotic fluid with its resultant closer application of the uterus to the fetus and the greater likelihood of bacterial invasion of the birth canal, is of prime importance. In our series 60.3 per cent of the patients had either an intact bag of waters or membranes ruptured less than six hours. Of the remainder, 17.2 per cent had membranes which had been ruptured twenty-five hours or longer upon admission to the hospital. Results for both mother and child are far too frequently affected seriously by a prolonged attitude of hopeful expectancy prior to hospitalization which eventually leads to unpleasant consequences, entirely avoidable in many instances if more intelligent methods had been employed. Neglected cases with their resultant retraction rings and ruptured uteri are admitted to every clinic frequently enough to impress upon everyone the consequences of a failure to make an early diagnosis and to properly treat this complication when it is encountered.

Many of the patients in this series were admitted to the hospital after being improperly handled. A prolonged period of labor, membranes ruptured for many hours, a variable amount of cervical dilatation, and a prolapsed extremity or cord characterized a number of admissions. Thus, the type of treatment of necessity varied tremendously, and many procedures were necessary which would have never occurred had an opportunity been available for the intelligent handling of the case from the start. External version was possible in 17 instances, internal podalic version and breech extraction was resorted to 87 times, or 57.6 per cent of the cases. Twenty-three cesarean sections were done, and 12 destructive operations were necessary. In 6 instances, spontaneous delivery occurred without interference on the part of the operator. These were in the presence of small and usually macerated

CASE 4 (83041).—A white, para 1-0-0-1, aged 30 years, had a negative serologic test for syphilis and a normal pelvis. The patient was brought to the hospital by her private physician. Her membranes had been ruptured for ten days according to him, and labor had begun twelve hours previous to admission. The labor pains which had been good since their onset slowed down somewhat, and a full ampoule of pituitrin was given. Within a few minutes, a hand protruded from the birth canal, and on admission to the hospital shortly thereafter, the uterus was tetanically contracted, the child presented transversely, and the heartbeat was absent. Deep anesthesia was administered and a Bandl's ring was palpated through a fully dilated cervix. Following a destructive operation, a full-term child was extracted with difficulty. Exploration of the uterus revealed a rupture in the lower segment. Hysterectomy was immediately performed. In spite of repeated transfusions and oxygen the patient did badly and died three days following operation.

Comment.—This is another example of the incorrect way to treat a transverse presentation. Failure to diagnose the presentation, the administration of pituitrin injudiciously, and the unwise attempt to deliver from below in the presence of a tetanically contracted or already ruptured uterus, all played a part in the tragic results in this case.

CASE 5 (32563).—A colored, para 6-0-0-6, aged 33 years, with a serologic test for syphilis negative and pelvis normal, was admitted to the hospital from the outpatient department with a transverse presentation and a prolapsed hand. On admission, the membranes had been ruptured twenty-seven hours, and the cervix was about two-thirds dilated, pains having begun shortly after the membranes ruptured. The patient was anesthetized, the cervical dilatation was completed manually and a premature live child was delivered with difficulty by internal podalic version and breech extraction. Twenty-five minutes later the patient began to bleed profusely, losing over 1,000 c.c. of blood. Oxytocics and intravenous fluids were given, and even though the bleeding ceased, severe shock developed quickly, and two hours from onset of the hemorrhage, the patient died. Autopsy was refused but post-mortem examination of the birth canal failed to reveal any laceration in the cervix or uterus.

Comment.—The various errors in the treatment of this patient, such as the expectant attitude in dealing with a transverse presentation, the prolonged labor and rupture of the membranes, the accouchement forcé followed by a version and breech extraction, all contributed to the death of this patient. One is inclined to suspect that a failure to diagnose a tear in the lower uterine segment occurred at the post-mortem examination.

CASE 6 (35978).—A colored, para 1-0-0-1, aged 19 years, serologic test for syphilis negative and pelvis normal, was sent to the hospital by her family physician with a history of her membranes having ruptured three days, and labor having commenced about thirty hours prior to admission. On vaginal examination, seven hours after the onset of labor pains, he discovered a shoulder presentation which he attempted to correct by pressure from below. Several hours later another vaginal examination revealed an arm prolapsed into the vagina, and the patient was hospitalized. The patient was at term, a transverse presentation was obvious on abdominal examination, the fetal heart was heard, and the uterus was tetanically contracted with evidence of a thinned-out lower uterine segment. The administration of oxytocics was denied. A classical cesarean section was done following which the patient ran a very stormy course, and died five days postoperatively of puerperal infection. Autopsy was not available.

Comment.—This case needs little comment to condemn about every step in her care, from the rupture of the membranes three days before admission, to the repeated vaginal examinations, the failure to diagnose a transverse presentation very much earlier, and the delivery by a classical section. In all fairness it should be said that since this case occurred seventeen years ago the laparotrachelotomy was not in vogue, but there was little excuse for not removing the uterus at the time of operation and in all probability a maternal death would have been avoided.

CASE 1 (10206).—A white, para 3-0-1-2, aged 28 years, had a negative serologic test for syphilis; pelvis was normal. A full-term fetus lay in the transverse position and after forty-seven hours of labor the cervix was 8 cm. dilated, and the membranes were unruptured. An internal podalic version and breech extraction was done with considerable difficulty; the child delivered up to the head when more difficulty was encountered. The head was finally delivered but the fetus was stillborn. Examination of the patient revealed a severe tear in the cervix extending into the lower uterine segment. A laparotomy was performed, revealing a tear into the right broad ligament, and a hysterectomy was immediately done. The patient stood the procedure well, had an uneventful convalescence, and was discharged from the hospital in fifteen days in good condition.

Comment.—The combination of poor prenatal observation, neglect during a long labor, and poor judgment at the time of delivery was indeed sufficient to account for the results obtained in this case. The incompletely dilated cervix was ignored and this probably accounted for much of the difficulty. Hysterostomy might have avoided the severe laceration and stillborn child. Only good fortune can be credited with a live mother following this type of unintelligent treatment.

CASE 2 (11130).—A colored, para 9-0-0-8, aged 38 years, serologic test for syphilis negative, pelvis normal, was admitted to the hospital from the outpatient department after having been in labor for thirty hours. The membranes ruptured spontaneously one hour after the onset of labor. The pregnancy was at term and the presentation was transverse. On admission, the cervix was found to be fully dilated and the elbow prolapsed into the vagina. A diagnosis of a Bandl's ring was made which seemed to relax under deep anesthesia. An internal podalic version and breech extraction was done without difficulty and a full-term live child was delivered. The third stage was normal, but on exploring the uterus routinely, a laceration was discovered in the lower segment which extended into the broad ligament. A hysterectomy was immediately done. The patient stood the operation well, but the puerperium was quite stormy. After seventeen days, both mother and baby left the hospital in good condition.

Comment.—Here again it is obvious that hopeful expectancy was depended upon with deleterious results. The version and extraction following a prolonged labor with ruptured membranes resulted in a rupture of the uterus. Correction of the transverse presentation early in labor by external version combined with the use of a binder or a scalp forceps might very well have resulted more favorably and placed the patient in less jeopardy.

CASE 3 (24962).—A colored, para 6-0-0-6, aged 33 years, with a serologic test for syphilis negative and pelvis normal, was admitted in labor. Labor began at 2:00 A.M., membranes ruptured at 6:30 A.M., and at 8:30 A.M. a hand prolapsed. She bled about 200 c.c. at this time and showed mild shock. On admission, it was found that there was a shoulder presentation, with the cervix fully dilated. There was some dullness in the left flank on percussion at this time. The fetal heart was absent and the general condition of the patient was very poor. Intravenous glucose and blood were given in an attempt to improve the patient's condition for operation, since a ruptured uterus or a premature separation was fairly obvious. The patient suddenly became pulseless and respirations labored. Following transfusion, she rallied considerably, and a full-term stillborn child was delivered by internal podalic version and breech extraction. Exploration of the uterine cavity revealed a rupture on the left side. Hysterectomy was immediately performed, but the condition of the patient was so poor that little hope existed for her recovery, and she died shortly after the operation was completed.

Comment.—Earlier recognition of a rupture of the uterus and elimination of the delivery by the vaginal route might have resulted differently in this case. This, of course, is not by any means a certainty, since the general condition of the patient was critical on admission to the hospital. Again, an early diagnosis of a transverse presentation followed by its correction if possible might have avoided much of the difficulty.

TREATMENT OF EXPERIMENTAL ANOXIA WITH CERTAIN RESPIRATORY AND CARDIAC STIMULANTS

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THE number of babies which die at birth in the United States approximates 80,000 annually; since an additional 30,000 die during the first day of life, from causes which are almost always natal in origin, the total infant mortality consequent upon the change from intra- to extrauterine life is about 110,000 yearly. The majority of these deaths are respiratory in their clinical picture. Most often, the baby simply does not breathe at birth, despite the fact that the heart is beating and despite attempts at artificial respiration and the use of respiratory stimulants. During recent years, this problem of apnea of the newborn has been attacked with special vigor; several important etiologic factors have been elucidated and various types of therapy suggested. Prominent among the latter are a number of reports recommending the use of medicinal respiratory stimulants, notably, "alpha-lobeline," "metrazol," and "coramine."

Modern interest in alpha-lobeline as a respiratory stimulant dates from 1915 when Wieland of Germany isolated the hydrochloride of lobelia in crystalline form; and subsequently the drug has enjoyed widespread use in such conditions as morphine and chloral poisoning, carbon monoxide asphyxiation, pneumonia, laryngeal stenosis and apnea of the newborn. Metrazol (pentamethylenetetrazol) and coramine (pyridine-beta-carboxydiethylamide) have also been recommended to combat apnea at birth, both being well known respiratory stimulants. The first published reference to coramine appeared in 1922 under the authorship of Lagier, and since that time almost 1,400 articles have dealt with various aspects of the drug. When employed in apneic newborn, these agents are usually injected directly into the umbilical vein, the dose ranging from one-sixth to one-third the adult dosage.

Although it might seem offhand that the value of alpha-lobeline, metrazol, and coramine in apnea neonatorum could best be determined in actual cases of this disorder, a number of factors renders such clinical observations of dubious reliability. In the first place, many apneic babies cry after thirty seconds or so, even though nothing whatsoever is done to them; naturally, had a drug been given in such cases, the initiation of respiration would have been credited, erroneously, to the therapy. In the second place, the causes of apnea at birth are various, a circumstance which renders the interpretation of treatment difficult. Finally, in the human newborn, rigorous and carefully controlled observations on the effect of any one therapeutic agent are almost impossible, since it is obviously mandatory to employ all recognized means of resuscitation in order to give the infant every possible

SUMMARY AND DISCUSSION

From these cases it can be seen that nearly all of the ruptured uteri and maternal deaths were unnecessary tragedies which probably would not have occurred had early diagnosis and proper treatment been the rule in each and every case. If space permitted, close scrutiny of almost every stillbirth in this series from the point of view of preventability would disclose a similar picture.

Careful study of every case leads one to the conviction that a very much lower morbidity and mortality rate would have been attained if certain basic principles had been observed. The most important of these are:

1. The recognition of the transverse or oblique presentation prior to or early in labor.

2. An attempt should be made to correct the presentation of the child by external version.

3. An abdominal binder or a Willett clamp where advisable can often be used to hold the child in its new position.

4. The dangers associated with internal podalic version and breech extraction should be realized and this operation avoided unless all the requirements are present for its proper performance, particularly a fully dilated cervix, lack of disproportion, a sufficient amount of amniotic fluid, and a sound uterus.

5. The more frequent use of the extraperitoneal section and hysterectomy when dealing with infected or potentially infected patients.

6. In the presence of a pelvis which is considerably contracted, particularly in the primipara, the elective cesarean section should be the operation of choice.

7. In certain indicated cases, decapitation is the most advisable procedure.

8. Intelligent antenatal and intranatal care will unquestionably result in the avoidance of many unnecessary fetal and maternal catastrophes which now occur frequently in the hands of those treating the transverse presentation by the method of hopeful expectation.

Blaisdell, Paul C.: Repair of the Incontinent Sphincter Ani, Surg. Gynec. Obst. 70: 692, 1940.

Advantage is taken of a direct attack on the anterior normal portion of the external sphincter rather than on that portion mutilated by operation and deformed by scar tissue, heretofore utilized. A reef is taken in the muscle through the vagina, so that the circumference of the whole muscle and of the anal outlet is diminished. Dependence is placed exclusively on this effect with entire disregard of the scar tissue.

This operation not only largely eliminates the basic sources of failure of the other operations but its advantages are strikingly positive as well: Disruptive infection is avoided in a large proportion of the surgical group by the substitution of clean vaginal approach rather than through the perianal skin. The procedure entirely obviates what is often the most difficult and yet essential step of the usual plastic operation, that is, accurate and adequate identification and dissection of the frayed ends of muscle buried in scar tissue. There are numerous instances in which after repeated clumsy rectal operations the scar tissue occupies such a large part of the anal circumference as to prohibit any possibility of success following removal of the mass. With this operation, on the contrary, the opposing factors of tension and stenosis are entirely controllable. Of course, replacement of over half of the circumference of the anus by scar tissue would impose unsurmountable limitation.

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they are entirely secondary and that the primary blood chemical change in apnea neonatorum is an extreme reduction in the oxygen content of the infant's blood.

Let us now consider, from the viewpoint of anoxia, the clinical behavior of these apneic babies. Since minor degrees of oxygen want increase the rate and amplitude of respiration, it is often forgotten that profound levels of anoxia (such as we have just described) produce the opposite effect, namely, absence of respiration. And it is seldom recalled in viewing a grave case of asphyxia at birth, with the slow heart rate, the white, cold skin of shock covered with meconium, and the limp extremities, how precisely, how completely this clinical picture duplicates the reaction of any organism to anoxia. In experimental animals, as well as in man, anoxia has been the object of intensive study for over a quarter of a century; on few other subjects has there been such complete agreement, for experimental anoxia produces a constant, clear-cut train of phenomena which may be reduplicated in the laboratory at will. The sequence of events will be recalled as follows. To mild degrees of anoxia the body reacts by increased respiration and accelerated heart rate; these presumably are compensatory mechanisms, the first designed to bring more oxygen to the blood and the second to deliver more oxygen to the tissues. With increasing anoxia, a point is reached when these mechanisms fail to supply oxygen in sufficient amounts for cellular oxidation and then, with remarkable suddenness, "the oxygen crisis" of the physiologists, or what is termed the "reversal" by Schmidt, takes place and after this, events occur rapidly. Consciousness is lost and respirations stop. Following respiratory failure there is an interval of from three to five minutes during which the heart continues to beat; but there is a marked slowing of the rate. In a typical case the slowing occurs in abrupt steps from 150 per minute before the crisis to 44 per minute in the posterisis phase. After respirations cease, sometimes a little earlier, the blood pressure falls until a systolic level of 15 to 20 mm. Hg is reached. Concomitant with the fall in blood pressure the skin becomes blanched and cold, as in shock. Early in the posterisis phase of experimental anoxia another important change occurs: the nerve muscle endings of skeletal muscle cease to function with complete collapse of that muscular system. This results, of course, not only in flaccid extremities but in relaxation of the sphincter ani. Finally, it may be noted that a few whiffs of oxygen or air, administered by artificial respiration, restore the animal at once to normal, provided this is done within three or four minutes of cessation of respiration. To summarize the picture of experimental anoxia in the posterisis phase, there occur in rapid succession loss of consciousness, cessation of respiration, marked slowing of the heart, fall in blood pressure with the white, cold skin of shock, and skeletal muscle collapse, causing general flaccidity of the extremities together with relaxation of the sphincter ani. Surely, few clinical conditions can be simulated so completely as can apnea neonatorum by experimental anoxia.

The close similarity, if not identity, between the severer forms of apnea neonatorum and experimental anoxia made it seem worth while

chance of survival; consequently drug therapy is often supplemented by other procedures, such as artificial respiration and skin stimulation, thus vitiating any conclusions which might be drawn between cause and effect.

If it is hazardous, then, to draw conclusions from the clinical use of these drugs, what can we say of the experimental approach? From every point of view, the picture of apnea at birth is the picture of anoxia. From a chemical standpoint, the blood is almost depleted of oxygen in the severer examples of this disorder. The variations in the blood oxygen met under various conditions at birth, together with certain other common alterations, are shown diagrammatically in Fig. 1.

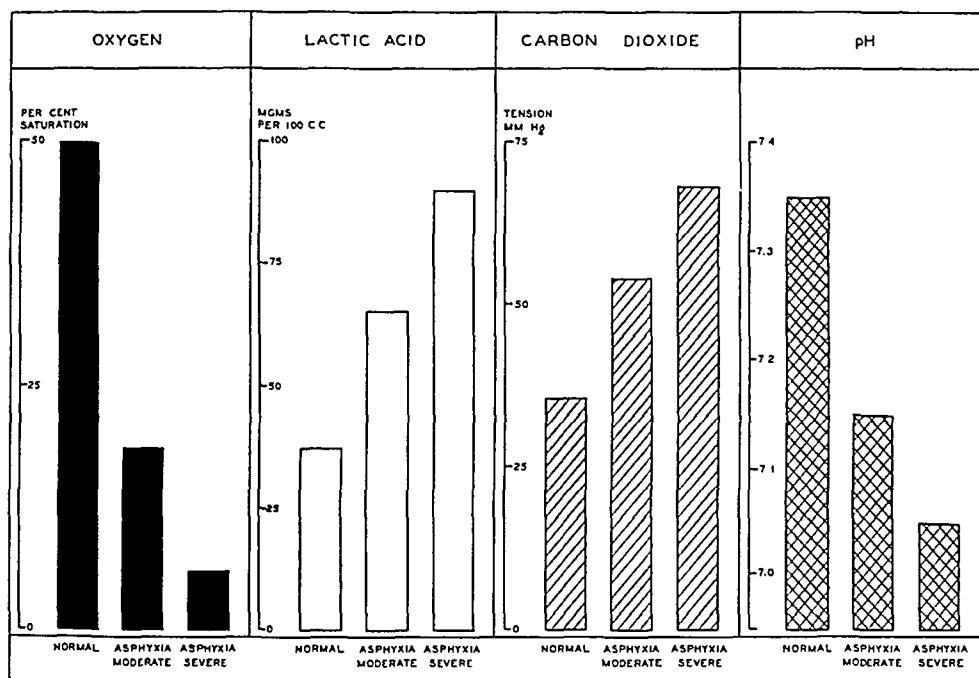


Fig. 1.—Showing the average blood chemical changes in moderate and severe asphyxia neonatorum. It should be noted in particular that the values for carbon dioxide represent the tension or partial gas pressure of free carbon dioxide and not the total carbon dioxide content.

It will be seen that whereas the normal saturation of the arterial blood of the fetus at birth is approximately 50 per cent, in apnea neonatorum the blood oxygen is reduced to levels which represent only one-fifth or even one-tenth of this value. That such low concentrations of oxygen are insufficient for fetal needs is clearly shown by the sharp rise in these cases of blood lactic acid, the characteristic product of anaerobic metabolism in the animal body. Consequent upon the marked increase in lactic acid, the pH of the blood falls to the lowest levels compatible with life. Partly because of an alkali deficit due to fixation of base by lactic acid and partly due to a primary carbon dioxide excess as the result of inadequate diffusion of this gas from fetus to mother, the tension, or partial pressure of free carbonic dioxide, rises to levels far in excess of normal. While these changes in the lactic acid, pH, and carbon dioxide tension of the blood are marked, it should be noted that

within a few seconds by artificial insufflation with oxygen. The temporary rise in blood pressure which followed the administration of the drug in this experiment is very possibly the result of pressor action by alpha-lobeline; but it was not a constant finding and was occasionally

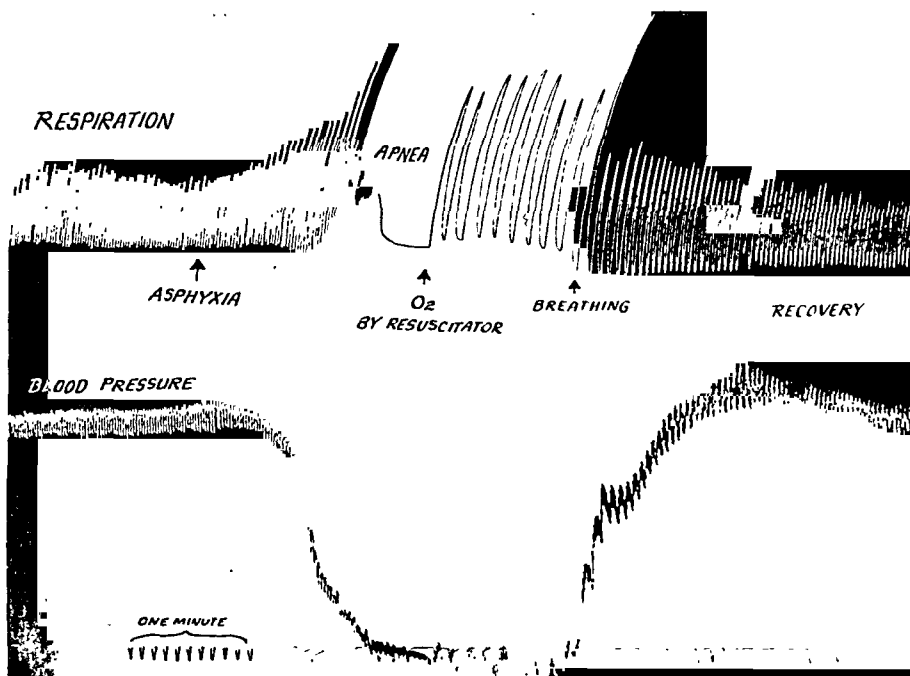


Fig. 2.—Showing behavior of respiration and blood pressure in experimental asphyxia, no stimulating drugs being administered. Resuscitation was effected by insufflation with 100 per cent oxygen as indicated by arrows.

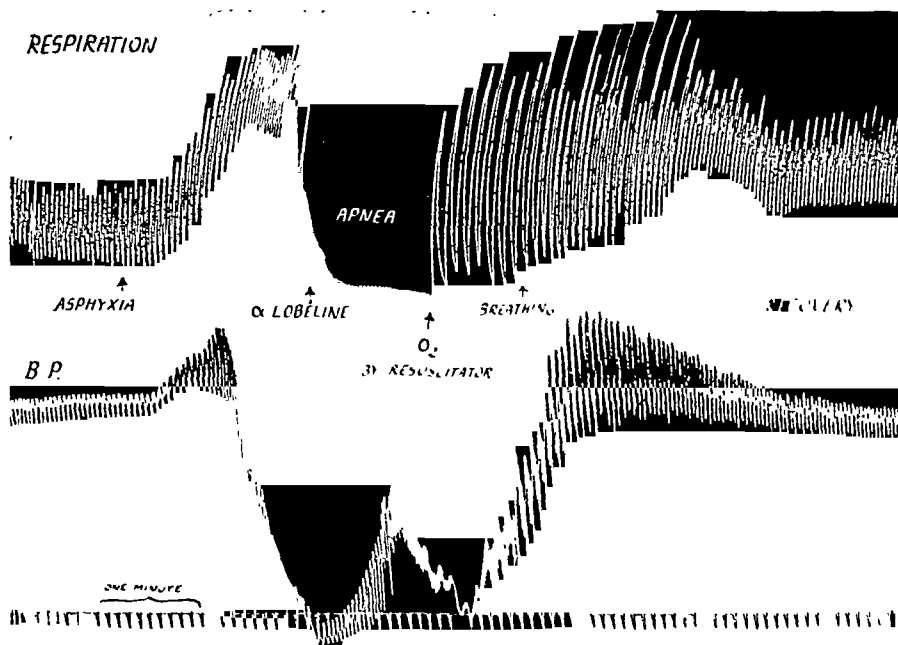


Fig. 3.—Showing failure of alpha-lobeline (3/20 gr. intravenously) to initiate respiration in the presence of anoxia. Breathing was readily established, however, by insufflation with 100 per cent oxygen, as indicated by arrows.

to study the value of alpha-lobeline, metrazol and coramine in the resuscitation of dogs which had been rendered apneic by anoxia.

METHODS

Dogs weighing between ten and twelve pounds were anesthetized lightly with chloroform and strapped to the table in the usual supine position. The trachea was exposed, opened, and a cannula inserted, through which nitrous oxide-oxygen anesthetic mixtures, and if necessary ether, were administered. Fluctuations in blood pressure were recorded in the usual manner by means of a cannula in the right femoral artery connected with a mercury manometer and slowly revolving kymograph.

Around the animal's chest and upper abdomen was placed a rubber bag which was secured in place by a loosely tied cloth casing. The bladder was inflated slightly and connected to a large tambour by means of a rubber tube, the connecting medium being air. To the rubber membrane was affixed a pointer which recorded the respiratory excursions.

Asphyxiation was accomplished in most experiments by allowing the dog to breathe 100 per cent helium. Because of its well-known ability to penetrate tissues quickly, this inert gas proved superior both to nitrogen and nitrous oxide in its ability to produce rapid and profound anoxia. In a few experiments, 95 per cent helium and 5 per cent carbon dioxide was used as the asphyxiating gas in order to meet the possible objection that the apnea produced was due to a "washing out" of carbon dioxide. The results attained with the latter gas mixture differed in no important way from those achieved by 100 per cent helium.

At the depth of the oxygen crisis blood samples were taken from the left femoral artery for oxygen determination. These showed oxygen levels which ranged between 2.3 and 4.0 volumes per cent; in severe apnea neonatorum, the oxygen levels of the umbilical vein blood vary between 0.5 and 4.0 volumes per cent. All drugs were injected either into the femoral vein or, when stated, into the carotid artery.

RESULTS

Kymographic tracings of the respiration and blood pressure in a typical case of experimental asphyxia are shown in Fig. 2. After thirty seconds of asphyxiation, an increase in the amplitude of respiration may be noted; within another thirty seconds, there is marked hyperpnea for a few breaths, but this is followed promptly by apnea. The fall in blood pressure in this instance is particularly marked. After approximately a minute of apnea, rhythmic insufflations of oxygen restore spontaneous respiration.

To what extent, if at all, may this picture be modified by the injection of alpha-lobeline, metrazol, or coramine?

Fig. 3 shows that alpha-lobeline (3/20 gr.), administered intravenously at the beginning of the apneic phase, exerted no effect whatsoever on the respiration, apnea persisting for a full minute after the drug had been given. It was nevertheless possible to re-establish respiration

The results in our experiments with metrazol are very similar, a typical example being shown in Fig. 4; metrazol (dosage 3 c.c.) failed to initiate respiration although this could readily be accomplished by insufflation with oxygen. The same temporary rise of blood pressure is observed here as was noted with alpha-lobeline. As may be seen in Fig. 5, our results with coramine were likewise negative, no effect on respiration being observed.

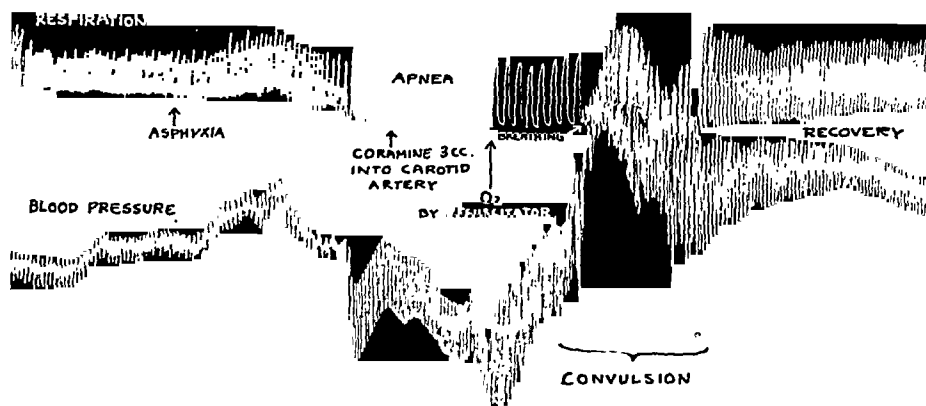


Fig. 6.—Showing failure of coramine (3 c.c.) to initiate respiration even when injected into carotid artery.

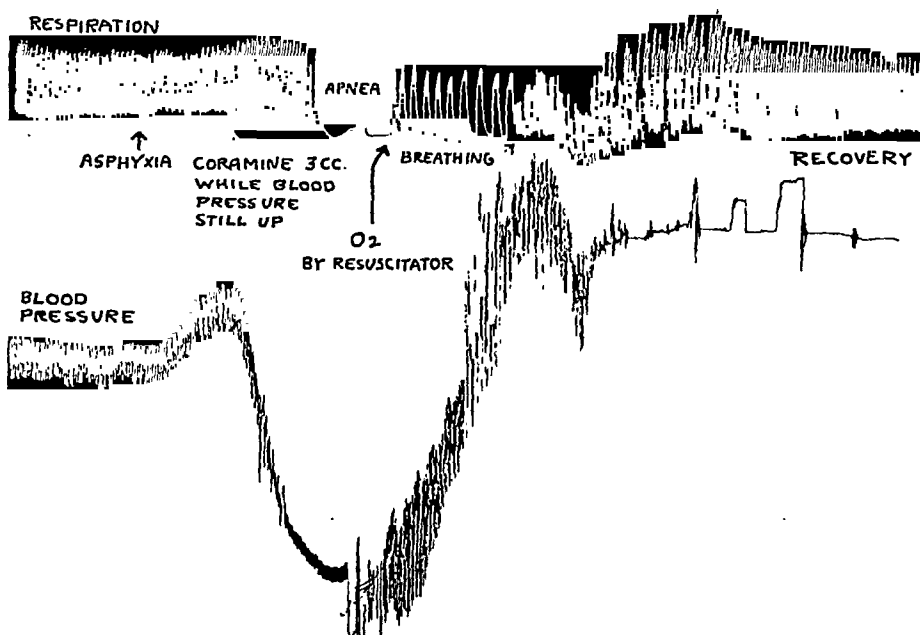


Fig. 7.—Showing failure of coramine (3 c.c. intravenously) to alter the usual picture of experimental asphyxia even when injected at a time when circulation was in good condition.

In all, some 15 such experiments have been carried out with each of these drugs, and in no instance have we been able to detect any effect on respiration in the presence of anoxia.

met in experiments in which no drug was given. However this may be, in the presence of continued apnea, the blood pressure quickly returned to its previous low level. The dosage employed in this eighteen-pound dog was the same per kilogram of body weight as that recommended in apneic infants.

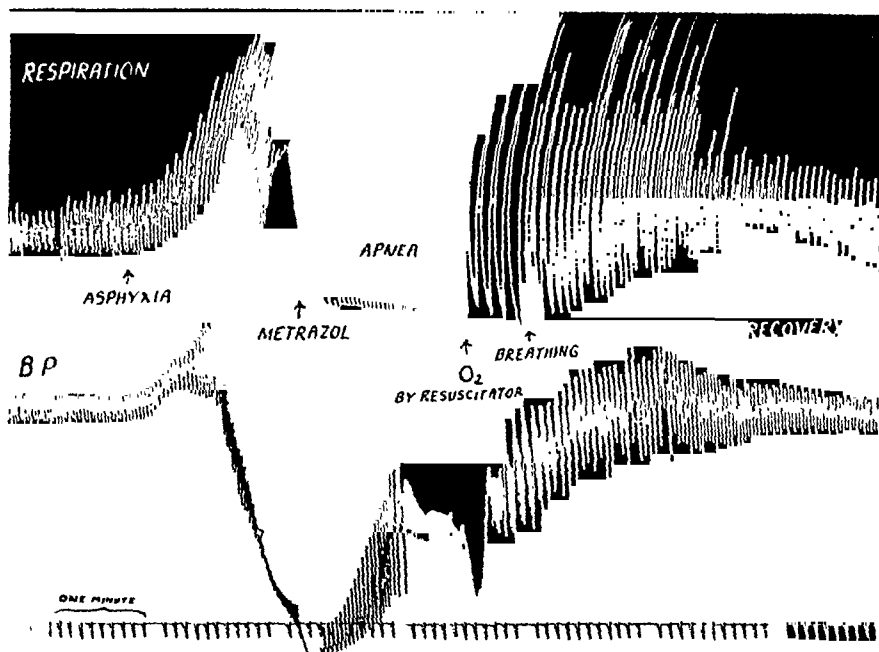


Fig. 4.—Showing failure of metrazol (3 c.c. intravenously) to initiate respiration in the presence of anoxia. Breathing was readily established, however, by insufflation with 100 per cent oxygen, as indicated by arrows.

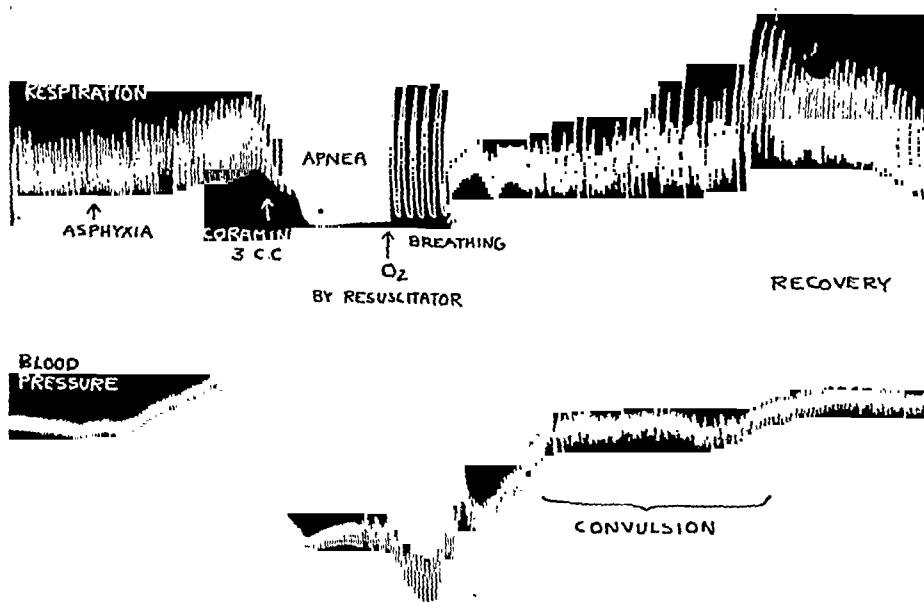


Fig. 5.—Showing failure of coramine (3 c.c. intravenously) to initiate respiration in the presence of anoxia. Breathing was readily established, however, by insufflation with 100 per cent oxygen, as indicated by arrows.

THE ENDOMETRIUM IN TUBERCULOUS PERITONITIS AND IN STERILITY*

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ENDOMETRIAL tuberculosis is usually regarded as a rare disease. However, it appears to be more common than is generally appreciated. Tuberculosis of the endometrium presents a number of interesting problems from the clinical as well as pathologic aspect, largely because there is no comparable tissue in the body. This is due to the fact that in the normal menstrual cycle the endometrium is constantly changing its histologic appearance until it finally sloughs at the beginning of menstruation.

Our work on this problem includes a careful study of the pathologic changes in the endometria of 75 uteri which had been removed in the course of surgical procedures. An attempt was made when possible to study recent specimens. Otherwise the cases were taken at random from the files.

REVIEW OF LITERATURE

Very little has been added to the literature concerning uterine tuberculosis since the excellent discussion of Williams in 1893. He expressed the opinion that tuberculosis of the uterus was nearly always secondary to tuberculosis elsewhere in the body and that it was usually associated with tuberculosis of the tubes from which the process extended to the uterus.

According to the statistics offered by various authors, genital tuberculosis has been observed in from 1 to 8.5 per cent of all cases of phthisis, among women, which came to necropsy. In 6,000 routine post-mortem examinations, Simmonds found tuberculosis of the female genital tract in 1.5 per cent of all cases. Williams found 5 cases of unsuspected tuberculosis of tubes and ovaries in the course of 137 laparotomies on women. Miller reported two instances of tuberculosis of the female genital tract in 68 cases in which pelvic laparotomy was performed, an incidence of 2.9 per cent. The exact incidence of tuberculous endometritis is not available because the uterus is not usually removed when no gross involvement is found. According to Jameson, it is probable that in 50 per cent of all cases of genital tuberculosis among women the uterus is involved.

Tuberculosis of the female genital tract appears to be essentially a disease of the childbearing age. Simmonds found that tuberculosis in that region usually occurred between the ages of twenty and forty years. It is extremely rare in children. Kelly in 1901 was able to collect reports of only 21 cases from the literature in which the patient was less than fifteen years of age.

It is generally agreed that evidence of tuberculous peritonitis can frequently be demonstrated when tuberculosis of the uterus and oviducts is present. Schramm, writing in 1882, stated that out of 34 women with genital tuberculosis, 21 had tuberculous peritonitis. Oppenheim noted it in 21 out of 23 cases. Osler stated that the tubes were affected in 30 to 40 per cent of all cases of tuberculous peritonitis.

Kiwisch, Rokitansky, Forster, and Cruveilhier have expressed the opinion that tuberculosis reaches the uterus from the peritoneum by way of the fimbriated end

*Abridgment of thesis submitted by one of us (Jensen) to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

But it may be objected that these drugs, injected at such low blood pressure levels, did not reach the brain. We have attempted to answer this criticism by injecting each of these drugs, in 3 c.c. of solution, directly into the carotid artery. An example of such an experiment is shown in Fig. 6, and it is readily apparent that the effect on respiration is again nil. Moreover, the same drugs have been injected in the course of asphyxiation but some fifteen or twenty seconds before the blood pressure fell; as shown in Fig. 7, the administration of such a drug, even when the blood pressure is still up, alters in no way the usual pattern of anoxic apnea, the whole train of events proceeding as usual despite the fact that the drug must have made the rounds of the general circulation.

In this series of observations on alpha-lobeline, metrazol, and coramine, convulsions were observed in over one-half of the experiments, but they occurred only after complete re-oxygenation of the blood. Examples of this phenomena are seen in Figs. 5 and 6. The convulsions were of a violent character and lasted from one to two minutes; they were observed following the administration of all three drugs, but occurred more frequently after metrazol. In view of the fact that these drugs are powerful central nervous system stimulants, these findings are not surprising. Indeed, psychiatrists use metrazol therapeutically for the express purpose of producing convulsions, and obstetricians who employ alpha-lobeline in the resuscitation of the newborn report that the babies so treated often exhibit opisthotonos. The fact that in these experiments, however, the convulsions occurred only after the blood had been restored to its normal oxygen content would seem particularly significant, for it can only mean that these drugs, although present in the circulation in convulsive concentrations, are impotent in the presence of anoxia.

It is always hazardous to carry over conclusions drawn from animal experimentation and apply them to clinical therapy. In the present study, moreover, we have ventured to assume that experimentally produced anoxia is identical with the graver types of asphyxia neonatorum. On the basis of the low oxygen shown by these babies, and also on the grounds that the phenomena they exhibit are so very similar to those manifested by animals in anoxic apnea, we believe that there is some justification for this assumption. If this premise is acceptable, it would seem clear that alpha-lobeline, metrazol and coramine have no place in the treatment of apnea at birth because their effect on respiration is nil in the presence of anoxia; and, as we have shown, the severe forms of apnea neonatorum are regularly associated with anoxia. In other words, our findings are in keeping with the viewpoint that the chief desideratum in the treatment of anoxia at birth is not stimulating drugs with their likelihood of convulsive action but, obviously enough, oxygen.

The authors are deeply indebted to Dr. Morris Rosenfeld, of our Department of Pharmacology and Experimental Therapeutics, and to Mr. Edwin Stewart, Jr., for valuable technical assistance.

miliary tuberculosis with or without formation of ulcerations, chronic diffuse tuberculosis and chronic fibroid tuberculosis; others have mentioned the ulcerocaseous, hypertrophic, and interstitial forms. Such classifications are based on the gross appearance and are of little or no practical importance from a clinical standpoint. No attempt was made in this series to classify tuberculosis into these groups.

RESULTS

Group 1. Tuberculous Endometritis Among Parous Women.—In one specimen from this group of 25 uteri, tuberculosis was found in the block of endometrium taken from the midportion of the uterus. Only two tubercles were found. In this case also there was bilateral involvement of the oviducts and of the left ovary, but the cervix was not involved.

Group 2. Tuberculosis of the Endometrium Among Sterile Women.—Among the 25 cases of primary sterility in which hysterectomy had been performed were 2 cases in which tuberculosis of the uterine mucous membrane was found on microscopic examination of the endometrium and endocervix. In both cases bilateral tuberculous salpingitis was present also. In one only, endocervical tuberculosis was found; in the other case only the endometrium was involved in the region of the right horn. In this latter case only 2 out of 4 sections from the same block revealed involvement. The reason for removal of the uterus in both cases was the presence of multiple fibromyomas. The tuberculosis was unsuspected on clinical examination. In both cases the involvement was only minimal.

There was no involvement of the myometrium or of the basal glands and no caseation of the tubercles in this group (Table I).

TABLE I. TUBERCULOSIS OF THE ENDOMETRIUM IN 25 CASES OF STERILITY (GROUP.2)

NO.	LOCATION OF TUBERCULOSIS	ENDO-CERVIX		ENDO-METRIUM		BASAL GLANDS INVOLVED	GRADE OF INVOLVEMENT	CASEATION	REMARKS
		MUS-CLE	MUCOSA	MUS-CLE	ENDO-METRIUM				
1	Endocervix only	0	+	0	0	0	1	0	Only 2 of 4 sections in same block contained tubercles
2	Right horn	0	0	0	+	0	1	0	Minimal

Group 3. The Endometrium in Tuberculous Peritonitis.—The third and final group of 25 cases includes all the cases of proved tuberculous peritonitis, in which the uterus was removed at the time of the diagnosis or subsequently at the Mayo Clinic. Of these 25 cases, tuberculous endometritis was demonstrated in 15, or 60 per cent (Table II; Figs. 1, 2, and 3). The only examples of caseation found in the entire series were in this group. Endocervical involvement occurred in 47 per cent of the cases. In all 15 cases the oviducts were tuberculous. In one case tuberculosis and adenocarcinoma Grade 1 of the cervix were present.

When the 18 cases of tuberculosis from the three groups are considered, in 14 there was involvement of the endometrium and in 7 involvement of the endocervical mucosa.

COMMENT

In the experimental production of tuberculosis, caseation does not appear in the tubercles in its early stages.⁸ However, the absence of caseation in tuberculosis does not necessarily prove that a given lesion is early, since tuberculosis can be demonstrated especially in lymphoid tissue, the lymph nodes and tonsils, in which there is a minimal amount

of the tube; they cited as proof the fact that in many cases the process was most marked in the fimbriated portion of the tube and that this was the most vascular portion of the tube as well.

Sterility is not an infrequent accompaniment of tuberculosis of the female genital tract. Greenberg found that in 60 per cent of his series of 200 cases of tubal tuberculosis there was a clinical history of sterility. He found that the uterine mucous membrane was involved in 45 per cent of the cases in which tuberculosis of the Fallopian tube was present.

Williams in routine histologic examinations noted that adnexitis was tuberculous in 8 per cent of all cases. The uterus was involved in 60 to 75 per cent and the ovaries in 40 to 45 per cent of the cases in which the tubes were tuberculous. Norris claimed that pre-existing inflammatory lesions apparently predisposed to the development of tuberculous salpingitis. In about one-third of his cases of tubal tuberculosis, another form of salpingitis preceded. He also claimed the puerperal state to be a predisposing factor. Granzow from animal experimentation found that pregnancy and especially the puerperium increased the general susceptibility of the genital tract to infection with tuberculosis.

METHOD OF STUDY

The 75 uteri which were chosen for this study were classed into three groups. The first group consisted of 25 uteri which had been removed surgically from women who had borne children and who were not suspected of having tuberculosis before operation. The second group consisted of 25 uteri surgically removed from women who had never borne children in spite of the fact that they were married and desired to have children. Tuberculosis was not suspected preoperatively in any of these cases. The third group contained uteri from women who had tuberculosis of the peritoneum which was verified by histologic examination. Hysterectomy was performed either at the time of the diagnosis of the tuberculous peritonitis or at a subsequent date.

In all cases one block of tissue was taken from each of four different locations in the uterine mucous membrane: right horn, left horn, mid-uterus (the wall halfway between fundus and cervix), and endocervix. A portion of the myometrium together with the full depth of the endometrium or endocervix was included in each block. Sections were made from each block of tissue and stained with hematoxylin and eosin. The blocks were of approximately the same size and generally two sections from each block were examined microscopically. The histologic presence of a tubercle containing the characteristic epithelioid cells with or without necrosis was considered sufficient for a positive diagnosis of tuberculosis. Foreign body giant cells or lymphocytes were not considered essential to the diagnosis of tuberculosis.

The involvement of endometrium and endocervix was graded as follows: Involvement was classified as of Grade 1 when a total of 1 to 2 tubercles were found in the sections examined; Grade 2 when there were 3 to 6 tubercles; Grade 3 when there were 7 to 12 tubercles present; and Grade 4 when more than 12 tubercles were present. In addition to the number of tubercles, other factors were taken into consideration, such as the number of sections involved, the location, spread and extent of the tuberculosis as well as the presence or absence of caseation.

Attempts have been made by various authors to classify the pathologic features of genital tuberculosis into several groups, such as



Fig. 1.—Tuberculosis of the endometrium. One tubercle is shown (hematoxylin and eosin, $\times 110$).

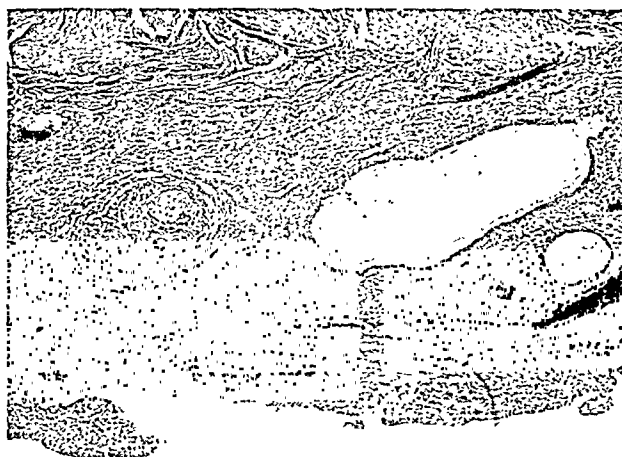


Fig. 2.—Tuberculosis of the endocervix showing two tubercles (hematoxylin and eosin, $\times 55$).



Fig. 3.—Tuberculosis of the endometrium. An area of caseation is seen (hematoxylin and eosin, $\times 55$).

TABLE II. TUBERCULOSIS OF THE ENDOMETRIUM IN 25 CASES OF TUBERCULOUS PERITONITIS (GROUP 3)

NO.	LOCATION OF TUBERCULOSIS	ENDO-CERVIX		ENDO-METRIUM		BASAL GLANDS INVOLVED	GRADE OF INVOLVEMENT*	CASEATION	REMARKS
		MUS-CLE	MU-COSA	MUS-CLE	ENDO-METRIUM				
1	All involved	+	+	+	+	+	4	+	Tuberculosis evident in all sections
2	All involved	+	+	+	+	+	4	0	Extensive tuberculosis
3	All involved	0	+	+	+	+	4	+	Only 1 tubercle noted in endocervix
4	All involved	+	+	0	+	0	4	0	Marked involvement of endocervix, others less
5	Both horns and mid-uterus	0	0	0	+	+	3	0	
6	Endocervix only	+	+	0	0	0	3	0	Many tubercles found
7	Both horns and mid-uterus	0	0	0	+	0	2	0	On routine sections only one suspicious area found
8	Mid-uterus	0	0	0	+	0	2	0	Tubercles found in one section only
9	Right horn	0	0	0	+	0	2	0	Tubercles found in one section only
10	Right horn	0	0	0	+	0	1	0	One tubercle only
11	Endocervix and mid-uterus	+	0	+	0	0	1	0	Tubercles seen in muscle only
12	Left horn	0	0	0	+	0	1	0	1 tubercle seen in 10 sections
13	Left horn	0	0	0	+	0	1	0	
14	Endometrium	0	0	0	+	0	1	0	
15	Endocervix only	0	+	0	0	0	1	0	

*Grading on basis of 1 to 4 in which 1 is slight and 4 extensive involvement.

of caseation and yet the lesion may be of many years' duration. In the present study caseation was seldom found in the endometrium or the myometrium. Furthermore the tubercles in this series were encountered most frequently in the superficial layers of the endometrium, less commonly in the basal layer and the myometrium. The endometrium is the only tissue in the body which is shed at regular intervals during premenopausal adult life. For this reason tubercles in the superficial

or both were found. Since the mucosa in this situation remains fixed, this might well serve as a source for the continuation of the infection. Endocervical tuberculosis has not received the attention that should be accorded it. In 2 cases in this series the endocervix only was involved.

SUMMARY AND CONCLUSIONS

In 2, or 8 per cent, of 25 cases of sterility studied, tuberculosis of the uterus was encountered.

The incidence of tuberculous endometritis in the 25 uteri from parous women studied was 4 per cent. However, in the 25 cases of tuberculous peritonitis studied, in which the uterus was surgically removed, tuberculous involvement of the uterus was found in 60 per cent.

Endocervical tuberculosis was found more frequently than has been described previously. It seems likely, therefore, that if more extensive histologic study were made of the endometrium in routine curettings and hysterectomies, the incidence of tuberculosis of the uterus would be found to be much higher.

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THE CONTRACTILE RESPONSE OF THE PREGNANT HUMAN UTERUS TO POSTERIOR PITUITARY EXTRACT

A STUDY OF 375 INJECTIONS RECORDED WITH THE LÓRÁND TOCOGRAPH
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IT IS well known that the uteri of pregnant women vary widely in their contractile responses to the administration of oxytocic drugs. There may be: (a) no response, (b) the inauguration of clonic contractions, or the augmentation of pre-existing ones, (c) a tetanic spasm, or (d) a combination of tetanic and clonic contractions. A tetanic reaction may be so intense and prolonged as to cause fetal death or even rupture of the uterus.

The unpredictability of the uterine reaction, and the seriousness of severe tetanic spasms indicate the need for more knowledge regarding the conditions under which untoward reactions are most likely to be observed. The advent of the Lóránd tocograph,¹⁻⁴ which affords, to a certain extent at least, a quantitative as well as a qualitative measure

layers of the endometrium are young, less than a month old. This no doubt partly accounts for the lack of caseation in this location. On the other hand tubercles when present in the myometrium and endocervix rarely show caseation in spite of the fact that neither of these structures is sloughed. This suggests an inherent capacity of the uterus to resist caseation. On the other hand, in 2 cases in which caseation was present in this group, there was a widespread involvement of practically all the structures in the uterus. This would suggest that when caseous tuberculosis is found in a specimen obtained at curettage, radical surgical treatment should be advised, because the process is likely to be extensive in the uterus.

It is also significant that tuberculosis was frequently not evident in most of the sections and that out of many sections from different parts of the endometrium and endocervix only one or two might give the pathologic picture of tuberculosis. In most instances the diagnosis of tuberculosis of the uterus is made on microscopic examination.

Tuberculosis appears to manifest itself primarily in the oviducts. In every case in which tuberculosis was demonstrated in the endometrium in this series there was tuberculous involvement of the oviducts. Hence, a diagnosis of tuberculous endometritis could have been considered tantamount, with few exceptions, to a diagnosis of bilateral tubal tuberculosis. This agrees with the opinion expressed by Norris and others. On the other hand tuberculous salpingitis does not necessarily imply that the endometrium is infected. In this series, the endometrium was involved in 60 per cent of cases in which tuberculous salpingitis was present. It seems likely that this figure would be higher if more exhaustive studies of the endometrium were made.

One of the most important considerations in genital tuberculosis is the site of involvement of the uterus. Obviously the condition in the uterus is not as serious when only the endometrium is involved as it is when the basal glands or the myometrial or endocervical tissues, which do not slough off at the time of the menstrual period are involved; in such cases, the probabilities of extension are much greater, the tuberculosis is of a more serious nature and is less likely to be controlled by conservative methods. When the endometrium is extensively involved, the myometrium almost always shows evidence of tuberculosis.

With the monthly desquamation of the endometrium, the question may well be raised as to why patients with tuberculous endometritis do not develop tuberculosis of the vagina or external genitalia. We found no instance of this in our series. It has been noted that in the experimental production of genital tuberculosis in guinea pigs, lesions of the vagina and external genitalia were uncommon, even following inoculation.

Tubercles on the serosal surface of the uterus are not necessarily a sign of tuberculosis of the uterus, but rather are evidence of tuberculous peritonitis.

An interesting finding in this group was the frequency of tuberculosis of the endocervical mucosa, often with extension to the musculature. In 7 cases, tuberculous lesions of the endocervix, cervical muscle,

A clonic response is indicated by the occurrence of rhythmically recurring waves inaugurated or augmented by treatment, without coincident elevation of the level of the valleys between the waves.

A tetanic response is characterized by an elevation of the recording line for a longer period than is required by a single clonic contraction. It is classified as being *incomplete* if it fails to interrupt the rhythm of the clonic contractions, and *complete* if one or more of these contractions do not occur. Examples of these responses appear in Figs. 1 to 3 inclusive.

Tension of Uterine Wall.—The tension of the uterine wall is measured in the following way: The tocograph is laid upon the most prominent part of the pregnant abdomen, with the patient supine. Early in pregnancy when the uterus is soft to the touch, and the tension of the uterine wall is low, the recording button on the bottom of the tocograph, which is in direct contact with the abdomen, meets no appreciable resistance from the underlying uterus, and consequently fails to displace the recording pen as the record is being made. If, on the other hand, the observation is made when the uterus is more tense, it displaces the recording button into the tocograph and thus changes the position of the recording pen upon the moving paper strip. Under the former conditions, for the sake of convenience, the uterus is said to exhibit no increase in the tension of its wall, whereas in the latter situation an increase in tension is said to exist. Furthermore, the degree of displacement of the writing pen appears to be proportionate to the degree of tension present.

RESULTS

A series of 96 patients, of whom 44 were multigravidas, received 375 hypodermic injections of obstetric pituitrin (291 treatments), or pitocin (84 treatments). Three hundred and forty-one treatments were given before, and 34 during labor. The dosages in minims were as follows: 0.5, 1.0, 1.5, 2.0, and 3.0. The number of observations per person is shown in Table I.

TABLE I. TREATMENTS PER PATIENT

Showing number of hypodermic injections of either obstetric pituitrin or pitocin received by each patient.

NUMBER		NUMBER	
TREATMENTS	PERSONS	TREATMENTS	PERSONS
1	42	10	2
2	14	11	2
3	7	12	2
4	4	13	1
5	5	14	0
6	4	15	1
7	6	24	1
8	2	25	1
9	2		
		Total	96

Incidence and Character of Response.—Of the 375 treatments (Table II), only 200 (53 per cent) elicited a positive response. Of the latter, 127 (63 per cent) were clonic, and 73 (37 per cent) tetanic. Of the tetanic ones, 23 were of the complete variety, being 11.5 per cent of all positive responses.

Parity.—Primigravidas responded less often than multigravidas, in the ratio of 46 to 77 (Table II), and their percentage of tetanic responses was higher (ratio of 39 to 31).

Labor.—Responses were more common *during* than before labor in the ratio of 76 to 51 (Table III), but *complete* tetanic responses were more common *before* than during labor in the proportion of 33 to 22.

of the contractile reaction of the pregnant uterus, affords a means for studying certain of the factors which modify the drug action.

The present study deals directly with the power of posterior pituitary extract to induce or modify the contractions of the uterus which take place during pregnancy and labor, and indirectly with certain factors which have a tendency to modify the contractile response. The object of the report is to indicate which of the factors studied are likely to lead to an unsatisfactory type of reaction. Such knowledge may be an aid in improving the results achieved when posterior pituitary extract is employed for the purpose of either inducing labor or improving the character of existing contractions.



Fig. 1.—Tracing 245. Tocographic record of uterine contractions. One minim of pitocin administered hypodermically at arrow. Note increase in frequency of contraction waves without elevation of the base of the waves. Typical clonic response.



Fig. 2.—Tracing 256. Tocographic record of uterine contractions. One minim of pitocin administered hypodermically at arrow. Note increased frequency of contractions accompanied by temporary elevation of the base of the waves. Typical incomplete tetanic response.



Fig. 3.—Tracing 956. Tocographic record of uterine contractions. One cubic centimeter of pitocin administered hypodermically at arrow. Note prolonged elevation of what would have been the wave base, if any had been present, together with obliteration of any signs of intermittent contractions for some time. Typical complete tetanic response.

MATERIALS AND METHODS

Patients attending the Maternity Department of the Hospital of the University of Pennsylvania and ones living at the Sheltering Arms Home acted as subjects. They were observed between March 22, 1939, and June 6, 1940. Each woman received one or more hypodermic injections of either obstetric pituitrin or pitocin (Parke, Davis & Co.) before, or during labor, or both. The resulting uterine contractions were recorded by means of a Lóránd tocograph. This is a simple mechanical device² for registering the movements of the pregnant uterus through the medium of the anterior abdominal wall, upon a strip of paper. The tocographic record was begun fifteen minutes or more before the injection, and was continued for at least thirty minutes thereafter. The contractile response was then analyzed with respect to the influence upon it of the following conditions: (1) parity, (2) the time in pregnancy that the treatment was given, (3) dosage, (4) the tension of the uterine wall.

Definitions.—A positive response is said to have occurred if a clear-cut alteration in the tocographic record took place within fifteen minutes of treatment time, which could not be charged to any other cause. Positive responses are classified as being clonic or tetanic, and if tetanic, as being either incomplete or complete.

TABLE IV. INFLUENCE OF DURATION OF PREGNANCY UPON RESPONSE

Showing influence of duration of pregnancy upon the uterine contractile response to posterior pituitary extract. Note: Greater response frequency late in pregnancy.

RESPONSE	DURATION OF PREGNANCY IN MONTHS																TOTAL
	4		5		6		7		8		9		10				
	TREATMENTS																
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
I Fre- quency: Treat- ment Response	1	100	8	100	8	100	19	100	46	100	83	100	176	100	341	100	
	0	0	0	0	0	0	4	21	12	26	41	49	117	66	174	51	
II Type: Clonic Tetanic	0	0	0	0	0	0	4	100	5	42	24	59	77	66	110	63	
	0	0	0	0	0	0	0	0	7	58	17	41	40	34	64	37	
	0	0	0	0	0	0	4	100	12	100	41	100	117	100	174	100	
III Tetanic: Incom- plete	0	0	0	0	0	0	0	0	6	86	11	65	26	65	43	67	
Com- plete	0	0	0	0	0	0	0	0	1	14	6	35	14	35	21	33	
	0	0	0	0	0	0	0	0	7	100	17	100	40	100	64	100	

TABLE V. INFLUENCE OF DOSAGE UPON RESPONSE DURING TENTH MONTH

Showing influence of dosage administered during tenth month of pregnancy upon uterine contractile response to posterior pituitary extract. Note: (1) Greater response frequency after larger doses, and (2) greater tetanic response frequency after larger doses.

RESPONSE	DOSAGE IN MINIMS										TOTAL	
	0.5		1.0		1.5		2.0		3.0			
	TREATMENTS											
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%		
I Frequency: Treatments Responses	9 8	100 89	57 28	100 49	29 21	100 73	48 37	100 77	32 23	100 72	175 117	100 67
II Types: Clonic Tetanic	8 0 8	100 0 100	22 6 28	79 21 100	11 10 21	52 48 100	26 11 37	70 30 100	11 12 23	48 52 100	78 39 117	67 33 100
III Tetanic: Incomplete Complete	0 0 0	0 0 0	3 3 6	50 50 100	8 2 10	80 20 100	6 5 11	55 45 100	9 3 12	75 25 100	26 13 39	67 33 100

DISCUSSION

The present data confirm the observations of many clinicians that uterine response does not always follow the administration of posterior pituitary extract during pregnancy. Using doses of 3 minims or less we observed no contractile response after 47 per cent of treatments.

On the other hand, even using these small doses, we observed a tetanic type of reaction following in approximately 37 per cent of treatments which exhibited any response whatever. In 11.5 per cent of instances the tetanus was of such a degree as to obscure any evidence of clonic activity (complete tetanic response). It is apparent, therefore,

TABLE II. INFLUENCE OF PARITY UPON RESPONSE

Showing influence of parity upon uterine contractile response to posterior pituitary extract. Note: (1) Higher response rate in multigravidas, (2) greater frequency of tetanic responses among primigravidas.

RESPONSE	PARITY				TOTAL	
	PRIMIGRAVIDAS		MULTIGRAVIDAS			
	TREATMENTS					
	NO.	%	NO.	%	NO.	%
I Frequency: Treatments Responses	284	100	91	100	375	100
	130	46	70	77	200	53
II Types: Clonic Tetanic	79	61	48	69	127	63
	51	39	22	31	73	37
	130	100	70	100	200	100
III Tetanic: Incomplete Complete	35	69	15	68	50	69
	16	31	7	32	23	31
	51	100	22	100	73	100

TABLE III. INFLUENCE OF LABOR UPON RESPONSE

Showing influence of existence of labor upon uterine contractile response to posterior pituitary extract.

Note: (1) Higher response rate during labor than before, and (2) higher incidence of complete tetanic responses before than during labor.

RESPONSE	TREATMENT TIME IN RELATION TO LABOR				TOTAL	
	BEFORE		DURING			
	TREATMENTS					
	NO.	%	NO.	%	NO	%
I Frequency: Treatments Response	341	100	34	100	375	100
	174	51	26	76	200	53
II Type: Clonic Tetanic	110	63	17	65	127	63
	64	37	9	35	73	37
	174	100	26	100	200	100
III Tetanic: Incomplete Complete	43	67	7	78	50	69
	21	33	2	22	23	31
	64	100	9	100	73	100

Duration of Pregnancy.—Irrespective of the dosages employed, no response was elicited prior to the seventh lunar month (Table IV); from then on the frequency increased progressively as pregnancy advanced; coincidentally the incidence of tetanic response decreased.

Dosage.—The influence of dosage was studied in the patients who were treated during the tenth month (Table V). All responses and tetanic ones alone were both more common following the larger doses.

Uterine Wall Tension.—The influence of uterine wall tension upon response in those patients observed during the tenth month of gestation is shown in Table VI. Responses were observed when there was an increase in uterine tension, twice as often as in its absence. Tetanic reactions also were more common in the presence of an increase in tension.

For a long time it has been known that large amounts of posterior pituitary extract may have serious consequences for either mother or child when employed during labor, but little if any attention has been directed to the part played by the existence of a high uterine wall tension in bringing about such unfortunate results. The present study emphasizes this point. Personal unpublished observations indicate that an oxytocic drug administered to a patient exhibiting a high uterine wall tension has little effective value in either inducing or augmenting clonic activity. Under such conditions the uterine muscle is already so much contracted that there exists little opportunity for further contraction—at least of the clonic variety. Consequently, when a patient possessing such a uterus receives a dose of an oxytocic drug, the result is likely to be a further tightening of the uterus to such a degree that any clonic activity is impossible. It follows from this that the effectiveness of an oxytocic drug is useful in proportion to the degree of relaxation exhibited by the uterus, and that if it is administered in the presence of a high degree of uterine wall tension, no good and perhaps harm may result. From this study, it would seem then that the obstetrician should utilize extremely small doses of posterior pituitary extract at all times, using small doses more often, rather than larger ones less frequently; that the tension of the uterine wall should be a guide in deciding whether or not to use the drug, and certainly if the tension is increased considerably, the dose, if given at all, should be extremely small. A subsequent study will deal with the question of uterine wall tension in greater detail, and the conditions under which it is most likely to appear.

SUMMARY

1. A series of 96 women at various stages of pregnancy and labor received 375 hypodermic injections of posterior pituitary extract not exceeding 3 minims per dose. During treatment a continuous record was made of their uterine contractions with a Lóránd tocograph.

2. Forty-seven per cent of treatments elicited no uterine response.

3. An increased frequency of response was noted more often: (a) in multigravidas than in primigravidas, (b) during than before labor, (c) later in pregnancy than earlier, (d) after the larger than the smaller doses of pituitary extract, and (e) when the uterine wall was tense than when it was relaxed.

4. The tetanic type of response occurred most often: (a) when the dose was large, and (b) when the uterine wall tension was high.

5. Complete tetanic contractions occurred most often: (a) when the uterine wall tension was high.

6. From this study the following conclusions are drawn: (a) That the amount of posterior pituitary extract employed, and the degree of tension of the uterine wall at the time of treatment, are two important factors to be considered when attempting to avoid an unsatisfactory type of uterine contraction during pregnancy and labor. (b) That during pregnancy and labor the most efficient type of uterine contraction is produced by the administration of small doses of pituitary extract. (c) That whether or not the drug should be employed, and how

TABLE VI. INFLUENCE OF UTERINE WALL TENSION UPON RESPONSE DURING TENTH MONTH

Showing influence of uterine wall tension upon uterine contractile response to posterior pituitary extract. Note: (1) Greater response frequency in presence of increased uterine wall tension, (2) greater frequency of tetanic contractile reactions in presence of increased uterine wall tension, and (3) greater frequency of complete tetanic contractile reactions in presence of increased uterine wall tension.

RESPONSE	UTERINE WALL TENSION				TOTAL	
	NOT	INCREASED				
	TREATMENTS					
	NO.	%	NO.	%	NO.	%
I Frequency:						
Treatment	111	100	64	100	175	100
Response	54	49	63	98	117	67
II Type:						
Clonic	51	94	27	43	78	67
Tetanic	3	6	36	57	39	33
	54	100	63	100	117	100
III Tetanic						
Incomplete	3	100	23	64	26	67
Complete	0	0	13	36	13	33
	3	100	36	100	39	100

that even following the administration of small doses of the extract the pregnant uterus is likely to experience a tetanic reaction. This is an important fact to bear in mind when administering posterior pituitary extract to a pregnant woman.

TABLE VII. SUMMARY OF DATA IN TABLES II TO VI (INCLUSIVE)

Summary of the effects of the factors described in more detail in Tables II to VI inclusive. Note: (1) How all factors increase the percentage of responses to posterior pituitary extract, (2) that increase of dosage and increase in tension of the uterine wall increase the percentage of tetanic response, and (3) that the increase in tension alone increases the percentage of complete tetanic responses.

FACTOR INFLUENCING RESPONSE	EFFECT UPON		
	RESPONSE FREQUENCY	TETANIC RESPONSE FREQUENCY	
		COMPLETE AND INCOMPLETE	COMPLETE
Multiparity	x ³	—*	—
Labor	x	—	—
Advancing pregnancy	x	—	—
Increase of dosage	x	x	—
Increase of uterine wall tension	x	x	x

X, Increase in response frequency.

—, No increase.

The data summarized in Table VII indicate the relative importance of the factors we have investigated. The two important ones are dosage and uterine wall tension because of the rôle they play in bringing about a tetanic type of reaction. The tension of the uterine wall appears to be the more important of the two. Not only does an increase in uterine wall tension increase the frequency of tetanic activity, but it also increases the chance that the tetanic contraction will be of the complete type.

In all, 10 patients received local refrigeration. There were 9 cases of cancer of the cervix, and 1 of cancer of the vulva. The majority of the patients had received maximal irradiation; the lesions were extensive and advanced, and secondary infection was marked in every case. In 4 of these cases, local refrigeration was discontinued after trial of six to twelve hours, because of the patient's failure to cooperate or her refusal to continue treatment. In the other 6 patients, local refrigeration was continued for 120 to 900 hours. Serial biopsies were studied. A report of these 6 cases follows:

CASE REPORTS

CASE 1.—A. J., white, single, aged 55 years, was admitted on Dec. 7, 1939, for a highly malignant carcinoma of the cervix; supravaginal hysterectomy had been performed thirteen years before. The cervix was very large with a deep central crater, and the parametria were thick, hard, and nodular. Biopsy of the cervix showed a plexiform anaplastic malignant growth comprised of sheaths of oval and polyhedral cells varying markedly in size and shape; cytoplasm was scant, the deeply hyperchromatic nuclei occupying the greater part of the cells; infection was present.

Local refrigeration was begun on December 9, and continued until January 17, at a temperature of 50° F. On January 11 moderate reduction in size of the mass was observed, and on January 20 she signed her release from the hospital. The mass had become much smaller, and pain had been somewhat relieved. She is known to have died at home three weeks later.

In the biopsy of December 21, cellular changes were first observed. Cytoplasm showed hyperchromatic degeneration, with poorly staining nuclei and indistinct cell outlines; mild necrosis was seen. On December 26, many broad areas and large vacuoles were seen, but no nuclei; vacuolization of cytoplasm was common, nuclei were swollen and poorly stained, and karyorrhexis was observed. In the biopsy of January 17, these changes were the most marked. Hydropic degeneration of cells and absence of nuclei were commonly noted.

CASE 2.—A. M., white, widow, aged 75 years, was admitted on Dec. 10, 1939, for extensive epidermoid carcinoma of the vulva. She had previously received 60 roentgen treatments. The labia and lower vagina were tightly distended by an irregular cartilaginous-like growth; the labia were fissured in several places, and foul purulent exudate exuded. Biopsy showed epidermoid carcinoma with small spindle cells and polyhedral cells invading the entire corium; narrow cords, large islands and invaginating papillary processes of squamous epithelial cells with keralinization and pearl formation were seen. The scant stroma showed extensive exudate and infection.

On December 14, refrigeration was begun with a combined vaginal and vulvar applicator. A temperature of 50° F. was maintained until Jan. 9, 1940. On December 17, swelling and induration had diminished and pain was relieved. Treatment was discontinued when oral temperature fell to 94° F., and she became drowsy; blood urea was 31 mg. per cent. She declined steadily and died in coma on Jan. 27, 1940.

Slight destructive changes were first noted in the biopsy of January 17. Biopsy on January 22 and 24 showed no change. At necropsy sections of the vulva showed marked necrosis and infection. The cell protoplasm was granular and hyperchromatic, and the nuclei were large. Superficial necrosis and infection were widespread.

CASE 3.—E. M., white, married, aged 44 years, was admitted on Jan. 2, 1940. She appeared to be in good condition, and was obese and comfortable. She had received 3,800 mc.hr. of radon eight weeks before admission. Biopsy of cervix showed columns of large and small epithelial cells, scant stroma, and pearl formation.

An attempt was made to conduct roentgen therapy and local refrigeration simultaneously, removing the applicator during x-ray treatment. Refrigeration was begun on January 20 and discontinued four days later because of moderate vaginal bleeding. Repeated hemorrhages then occurred and five transfusions were neces-

much should be used, during pregnancy or labor should not be decided without considering the degree of tension of the uterine wall.

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LOCAL REFRIGERATION IN GENITAL CANCER*

A REPORT OF TEN CASES

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THE work of Smith and Fay,^{1, 2} in refrigeration of cancer patients deserves attention, since their investigations covered a fair amount of clinical material and were supported by laboratory experiments and biopsy material which showed regressive cell changes. The idea had grown out of their observations on the effects of lowered temperatures on the rate of growth in plant and animal life. Freezing was found to be safe, for if the temperature was later raised to a normal level, growth was resumed unaltered. However, if low temperatures were maintained, cells were found to die, or degenerate, or produce cells which could not survive. Normal cells were said to survive a lower subnormal temperature than tumor cells, thus permitting the application of refrigeration for therapy. Pain was promptly relieved and the size of the tumor reduced.

A large number of women are admitted to Kings County Hospital with genital cancer so advanced that, except for relief of pain and nursing care, there is little to be done for them. For this reason we were desirous of giving refrigeration a trial. It appeared to us that for women with advanced pelvic carcinoma, particularly those who had been more or less completely irradiated elsewhere, any therapeutic measure which might possibly improve their status, or even relieve their pain, deserved serious consideration.

Local refrigeration was begun in November, 1939, with the intention of adding general refrigeration later. Our first equipment was a water pump which drove water through a metal coil immersed in a solution of salt and ice, then through rubber tubing into a hollow metal applicator designed and shaped to cover the lesion as completely as possible. Flow was continuous and temperatures were fairly well maintained by constant attention to the ice and brine solution. A little later very satisfactory equipment with automatically controlled temperature was generously loaned to us.† Applicators were devised by us to meet various conditions.

*Read at a meeting of the Brooklyn Gynecological Society, October 4, 1940.

†Wallace and Tiernan Products Incorporated, Belleville, N. J.

Biopsies showed no degenerative changes. On July 9, cell outlines in the cords of malignant cells were indistinct, the nuclei varying in size, shape, and staining intensity. Later biopsy showed nothing of interest.

COMMENT

In May, 1940, Lawrence W. Smith³ emphasized the experimental nature of the Temple University studies and stated that no patients had ever been accepted for treatment with expectation of a favorable outcome, but only for relief of pain and clinical study of the effect of low temperatures upon the life of cancer cells. Both Fay and Smith have warmly recommended the use of low temperatures as an adjunct to present methods of treatment, since they have continued to observe important cell changes in cancer. They found that whenever it had been possible to apply apparatus to the lesion so that the approximate delivered temperature would lie between 40° and 50° F., no case was observed in which striking regression of the tumor mass did not occur. Pain was consistently relieved in their cases.

Our cases are too few in number to warrant definite conclusions. It is well known that local cold will cause death of tissue, if the temperature is low enough and maintained. That there is a critical temperature which will bring about destruction of cancer cells without harm to normal cells is possible. It is clear that effectiveness of local refrigeration therapy must depend upon discovery of this optimal temperature, complete coverage of the lesion and satisfactory maintenance of temperature control in the entire depth of the diseased area. Construction of mechanical apparatus intended to cover the deep and wide parametrial outgrowth of carcinoma of the cervix is difficult and the penetration depth of the delivered temperature is unknown.

The implications of proximity of the bladder, rectum, and ureter must be seriously considered. The effect of previous irradiation on the pelvic tissues further complicates the problem. Occlusion of one or both ureters with consequent impairment of renal function is commonly associated with carcinoma of the cervix. There is no evidence, of course, that destruction of the ureter in two of our cases was due to refrigeration, yet it is an infrequent finding. Ewing⁴ says: "The natural termination of most cases of uterine cancer is through uremia from occlusion of the ureters. . . . These important structures are commonly invaded from without through the parametrium, and while the wall long resists destruction, partial or complete occlusion is readily established by inflammatory processes. The ureter may also be invaded by extension through the bladder wall, and it may be occluded by inflammation extending upward from the bladder. Dilatation of the ureter, hydronephrosis, and chronic nephritis with gradual suppression of the renal function regularly follow."

Regression in size of the tumor mass seems encouraging, but in cancer of the cervix, it is relatively unimportant. Pain may be relieved by other methods with much less danger.

SUMMARY

Ten patients with advanced genital cancer, 9 cases of carcinoma of the cervix, and 1 case of carcinoma of the vulva received local refrigeration.

sary. Roentgen therapy was discontinued. On March 26 she had improved so much, that refrigeration was resumed. After twelve hours, with local temperature at 60° F. oral temperature fell to 94° F., and she became very drowsy. She died in coma five days later, blood urea rising to 64 mg. per cent.

At necropsy the posterior fornix was found completely necrotic with a rectovaginal and a vesicovaginal fistula; the ureters were patent, but narrowed. Sections of the pelvic tumor showed sheets and columns of large epithelial cells supported by a very scant amount of connective tissue, and surrounded by broad zones of necrosis, the nuclei were large, and the cytoplasm granular. Sheets of tumor cells were present in the body of the uterus.

CASE 4.—F. F., white, single, aged 40 years, was admitted on Feb. 17, 1940. She had received full irradiation seven months before. Biopsy had shown epidermoid carcinoma of the cervix, Grade II. Her urine showed numerous pus cells, and the blood urea was 46 mg. per cent. Vaginal examination showed a large crater about one inch from the introitus, involving the entire cervix and vaginal vault. The pelvis was filled bilaterally and posteriorly by a dense nontender mass. Urography showed moderate right hydronephrosis; function of the left kidney was nearly absent.

Refrigeration was begun on Feb. 24, 1940, and discontinued on March 2, because of marked edema of the labia and sloughing areas in the lower third of the vagina. An average temperature of 48° F. was maintained during this time. On April 15 refrigeration was resumed, and continued until April 22, with vaginal temperature maintained between 40° F. and 50° F. During the second trial of therapy, she became drowsy and confused, and died in coma nine days later. Blood urea at that time was 71 mg. per cent.

Biopsy on March 9 showed a broad zone of squamous epithelium covered with a thin layer of keratin. In other areas the dense anaplastic squamous cells showed indistinct cell outlines, scant cytoplasm, and nuclei which varied in size and staining characteristics. The stroma was hemorrhagic, and contained many round cells and plasma cells.

At necropsy the entire vaginal vault was necrotic, with a rectovaginal fistula. The left ureter was destroyed just proximal to the bladder, with its separated ends entering directly into the pelvic crater. Section of the tumor tissue showed irregular cords of epithelioid cells invading the cervix and uterine corpus. In many cells the nuclei were hyperchromatic, in others the nuclei were pale and vacuolated.

CASE 5.—J. M., white, married, aged 48 years, was admitted on Jan. 10, 1940. Irradiation was incomplete. On vaginal examination there was a large stony-hard irregular mass about the cervix, with a deep central crater. Urography showed complete closure of the right ureter, and stenosis of the left ureter with hydronephrosis. On biopsy of the cervix extensive epidermoid carcinoma Grades I and II was found with cells varying in size, shape, and staining quality, containing moderate cytoplasm and large hyperchromatic nuclei; evidence of severe infection was present.

Refrigeration was begun on January 12 and continued between 50° F. and 55° F. until January 16 when the patient became euphoric and disoriented. On February 24 a severe acute suppurative parotitis was incised and drained with recovery of a hemolytic *Streptococcus aureus*. Her condition became steadily worse, with death in coma on March 12. Blood urea rose progressively, finally reaching 320 mg. per cent. The size of the pelvic mass remained unchanged.

The last biopsy on Jan. 25, 1940, showed epithelioid cells with scant cytoplasm and very large nuclei; cell outlines were indistinct and vascularity pronounced.

CASE 6.—M. G., colored, married, aged 31 years, was admitted on June 22, 1940. The pelvis had been fully irradiated four months before. Pelvic examination showed a large crater in the vaginal vault, surrounded by nodular cartilaginous-like parametrium. The right kidney was hydronephrotic. Biopsy showed an epithelioid cervical carcinoma of high malignancy with evidence of infection.

Refrigeration was begun on July 5 and continued at 55° F. until July 15 when the patient became very drowsy. On July 17 she died in a convulsion, with blood urea steadily rising to 67 mg. per cent.

weeks. The present group consists of those who obeyed instructions to the extent of coming back on the day on which the postoperative clinic is held. It is unavoidably selective, being probably overweighted by those who did not feel that they had made a proper return to health. These would, no doubt be more inclined to seek the clinic than those who felt well and who, therefore, would be less likely to take the time for a procedure which would seem to them unnecessary. For this reason the proportion of morbidity shown here is probably considerably higher than would be found could the entire original series be interviewed and examined.

Patients were interviewed by the author and examined by the resident and visiting staff of the Bellevue Gynecological Service detailed to the postoperative clinic. Twenty-two of the 100 patients had admitted illegal induction; 8 had had therapeutic abortions; 70 had denied voluntary interference.

The great majority (89) of these patients were seen from three to six weeks after leaving the hospital. The account they gave of their behavior and emotions had altered considerably in this time.

Two of those who had previously admitted attempts to rid themselves of the fetus by taking supposedly abortifacient drugs, denied such attempt when seen at the clinic. Conversely, two who had denied induction subsequently admitted it. We were surprised not to find more changes in the history relating to induction.

TABLE I. CHANGES IN ATTITUDE TOWARD ABORTION

ATTITUDE AT HOSPITAL INTERVIEW	TOTAL	ATTITUDE AT FOLLOW-UP INTERVIEW				
		REMORSE	REGRET	RELIEF	SATISFAC- TION	INDIFFER- ENCE
Remorse	1	--	--	1	--	--
Regret	53	--	32	6	5	10
Relief	16	--	5	6	2	3
Satisfaction	9	--	2	1	6	--
Indifference	12	--	5	3	2	2
No record	9	--	2	4	2	1
Total	100	--	46	21	17	16

Much greater changes occurred in these patients' expression of their subjective attitude toward the abortion, toward their sexual partners and toward coitus. Table I shows that, while a few who had at first been pleased with the untimely termination of pregnancy afterward came to regret it, the general trend with time was toward relief and satisfaction. This may be due to the human tendency to accept *le fait accompli*. One-third of those who expressed satisfaction, relief, or indifference, at the same time complained of mental depression, a feeling of general "blueness," which dated from their recent illness. The attitude toward the sexual partner changed in a manner contrary to what one might expect. Of the 70, who at the time of the abortion expressed love for the partner, 15 had changed to mixed emotion or dislike by the time of the follow-up interview. In 13 cases the sex relationship which had been responsible for the pregnancy had been terminated with feelings of dislike and repugnance on the part of the woman.

tion therapy. In 6 cases the duration of therapy was 96 to 900 hours. Temperature was maintained between 40° F. and 50° F. in 1 case, at 50° F. in 3 cases, at 50° F. to 55° F. in 2 cases, and 60° F. in 1 case. Control of temperature was satisfactory.

Notable diminution in size of the tumor mass was observed in 3 cases, and pain was relieved in 2 cases.

Serial biopsies showed cellular degenerative changes in only 1 case. Marked necrosis of the cancerous refrigerated area was found at necropsy in 3 cases, in 2 of which fistulas were present with complete destruction of the ureter. Death occurred in coma in 4 cases, and it is our opinion that death was hastened by local refrigeration therapy.

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III. MEDICAL STATUS AND PSYCHOLOGIC ATTITUDE OF PATIENTS FOLLOWING ABORTION*

A FOLLOW-UP STUDY OF 100 CASES

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MUCH is said of the aftereffects of abortion, but little is known. It has been shown that active treatment of incomplete abortion shortens the time of hospitalization and permits the patients to resume their usual occupations earlier than does palliative therapy. Many advocates of the latter method of treatment maintain, however, that curettage is more likely to be followed by abnormalities of menstruation, chronic invalidism, and sterility. This view is always brought forward in discussion after any paper which presents a series of cases actively treated. That *immediate* morbidity and mortality are not increased by operation has been repeatedly demonstrated. We have been unable, however, to find any report in the American or English literature which throws any light on the *remote* results of curettage for incomplete abortion.

This is a report of a follow-up study of 100 patients seen at the Bellevue Hospital Gynecological Clinic a short time after hospitalization for illness associated with the early interruption of pregnancy. These women had all been interviewed previously by me, having been included in the series of 537 cases reported earlier.¹ On discharge from the ward all 537 were instructed to return to the Clinic for check-up in four

*Aided by a grant from The National Committee on Maternal Health, Inc.

Retroversion is discovered in about 20 per cent of nulligravidas examined routinely without reference to uterine symptoms. In a series of 372 routine pelvic examinations on a group, roughly comparable to the present series in age and parity, but differing in that it was selected for the denial of ever having undergone any type of abortion, the proportion which showed no demonstrable deviation from pelvic normality was 32 per cent, or slightly less than found here. In the same study, a group of 128 who gave a history of spontaneous or induced abortion presented only 25 per cent who could be said to have perfectly normal pelvic organs. The treatment the latter group received at the time of abortion is not known. A follow-up study on a series of patients treated palliatively would be of great value for comparison.

The author wishes to express her indebtedness to Dr. William E. Studdiford for his cooperation and encouragement without which this study would have been impossible.

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OBSERVATIONS ON THE POSSIBLE RELATIONSHIP OF DIET TO THE LATE TOXEMIA OF PREGNANCY

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IN RECENT years the idea has been advanced that diet and nutrition may bear a definite relationship to the development of the late toxemias of pregnancy. Ross¹ found that in North Carolina the prime factor in maternal mortality was toxemia and that the number of cases of toxemia among ill-nourished obstetric patients was out of all proportion to that found among their more fortunate sisters.

In our southeastern states, deaths from eclampsia² are more frequent in proportion to live births than are such deaths in our more prosperous northern states. It has accordingly been assumed that some factors in this area predispose to a development of a disproportionate number of cases of toxemias during the latter months of pregnancy. The number of toxemias admitted to certain obstetric hospital services in the south is high, but it is difficult to get accurate figures from their prenatal clinics showing the percentage of toxemias to pregnancies of entire populations. The many deaths due to eclampsia do not necessarily result from an increased rate in the development of toxemia, but to inadequate prenatal care. If one can show that far more toxemias of pregnancy develop in one area than in another, a comparison of eating habits, mode of life, etc., may well shed some light on their origin. If, for example, one could find in neighboring communities persons living under generally similar conditions, differing only in one or two particulars, but with a strikingly different incidence of pregnancy toxemias, an investigation of their variances might well be illuminating. To us it seems that valuable information may result if studies can be made for comparison of rates of

The attitude toward coitus had changed even more markedly in the same direction. Of 68 women who had stated in the hospital that they found pleasure in the act, 22 expressed indifference and 10 dislike after return to the home environment. Fifty-seven had resumed coitus when interviewed; 43 had not. Only 57 had refrained until one month or more postabortum.

As stated in an earlier report every effort was made to impress these patients with the importance of postponing pregnancy for a time, and directions were given for reaching the birth control clinics nearest their homes. That this effort had little influence is shown by the fact that of the 57 who had resumed coitus only 60 per cent were taking any precautions to prevent pregnancy. None had visited a clinic. One was referred to the Prenatal Clinic, three months pregnant, four months after a self-induced abortion. The majority of these women eagerly reiterated their wish to be referred for birth control and were again painstakingly directed to convenient clinics.

The management of the original 537 patients has been outlined in the earlier report. Of the 100 who figure in this follow-up study, 95 had been curetted, and 5 had undergone therapeutic hysterotomy and Pomeroy sterilization.

TABLE II. SYMPTOMS (PRESENCE BEFORE ABORTION DENIED)

Total cases	100
No complaint	23
Weakness	52
Tiredness	51
Abdominal pain	33
Leucorrhea	32
Depression	30
Backache	30
Constipation	22
Abnormal bleeding	19
Urinary dysfunction	15
Headache	8
Nervousness	2
Fainting	2

TABLE III. PELVIC PATHOLOGY

Total cases	100
No gynecologic pathology	38
Retroversion uteri	23
Uterus enlarged	9
Uterus soft	3
Cervical erosion	11
Endocervicitis	9
Adnexal or parametrial thickening	2
Adnexal or parametrial tenderness	7
Adnexal mass	5
Cystic ovaries	5
No record of pelvic examination	9

Tables II and III show the incidence of complaints and of pathology found at pelvic examination. While only 38 were pronounced entirely "negative," in most instances the abnormality found was of minor degree. Nearly all the erosions, for example, were described as "slight."

who did not have toxic albuminuria or hypertension on consecutive prenatal visits, but who did have symptoms sufficiently marked to warrant their inclusion: 3 in the mild group, 1 severe, and 2 with eclampsia. The average number of prenatal visits for these three groups during the toxic period was as follows: mild, 5.5, severe, 12, and eclamptic, 2.2.

In terms of blood pressure changes, there were 80 patients in whom the blood pressure ascended from 30 to 50 points to reach the given toxic level of 140. There were 28 patients with blood pressures above this point when first seen. There were 14 obviously toxic patients with blood pressures below this point during their entire toxic period. There were 13 patients in the hypertensive group whose pressures dropped below 140 prior to delivery, only 2 of these were not toxic at the time of delivery.

There were 76 patients with albuminuria, 28 with plus one albuminuria, 48 with plus two to plus four albuminuria.* In addition to those with toxic hypertension and with albuminuria, there was one patient with a toxic psychosis, which was due to pyelitis of pregnancy. This is the only instance in which a toxic state was secondary to pyelitis of pregnancy. There were 82 patients with associated edema, while 93 manifested toxic symptoms.

Among those with hypertension and albuminuria are included 20 patients whose toxic state was superimposed on a definite chronic nephritis or chronic hypertension, 8 and 12, respectively. This incidence probably does not include all such cases, as there is a lack of adequate information on the group in the nonpregnant state. There were 7 patients in whom the toxic state was repeated one or more times. These individuals accounted for 11 cases of toxemia.

Of the 10 cases of eclampsia, 8 appeared in the intrapartum period, two in the post-partum period. All were of an acute fulminating nature with a toxic period of from two days' to two weeks' duration (9 patients one week or less, 1 patient two weeks' duration). Seven of these patients had prenatal care of from three to twenty weeks prior to the toxic period, while 3 were toxic when registered.

The various time factors of the toxemia group were tabulated to show the duration of the gestation at the time of registration, the duration of the toxic period, and the calendar months involved. One-half of the patients registered from the tenth to the twenty-sixth week of their pregnancy. The other half registered after the twenty-sixth week. The average duration of the gestation at the time of registration for the entire group was 26.3 weeks, and for the toxic group, 25.7 weeks (mild, 25.7 weeks; severe, 24.9 weeks; and eclamptic, 30.4 weeks). The duration of the toxic period ranged from 21 weeks to less than 1 week, with the average for the entire group 4.9 weeks, and for the particular classifications: mild, 5.5 weeks; severe, 4.7; eclamptic, less than 1 week. In all but 8 patients the toxic period persisted until the termination of the delivery.

To show the seasonal incidence of this toxic group, the calendar year was divided into four equal periods: winter (December-February), spring (March-May), summer (June-August), and fall (September-November). When the toxic periods were arranged according to their

TABLE II. SEASONAL INCIDENCE OF TOXEMIA (PATIENTS WITH TOXEMIA)

	WINTER	SPRING	SUMMER	FALL
Mild	21	38	11	6
Severe	6	12	16	2
Eclamptic	6	2	2	0
Total	33	52	29	8

*Test done routinely on freshly voided specimen. Plus one albuminuria up to the point where the solution becomes opaque.

toxemia and living habits of different population groups, in areas of states that have a high incidence of eclamptic deaths.

The present study concerns itself with a rural, almost wholly white population in the hills of southeastern Kentucky, cared for entirely by the Frontier Nursing Service. A population of between 8,000 and 9,000 people, living in a relatively inaccessible territory of 700 square miles, is cared for by a physician (the author) and about 20 well-qualified nurse-midwives. There is no physician other than the Medical Director of the Service in the entire area. The Service maintains one hospital of 20 beds. From Sept. 3, 1925, until Jan. 11, 1940, we have cared for 4,004 regular registered obstetric cases, with a maternal mortality of 1.25* per 1,000 deliveries. It is on these cases that this study has been made. In normal cases, prenatal examinations have been made monthly from the date of registration for the first six months of pregnancy, bi-monthly for the next two months, and weekly for the last month of pregnancy. The delivery is usually conducted by the nurse-midwife in the home. Post-partum calls are made (depending on the distance from the nursing center) daily or every other day for the first ten days, and then weekly until the end of the month.

TABLE I. INCIDENCE OF TOXEMIA*

	MILD	SEVERE	ECLAMPTIC	TOTAL
Primigravida	9	12	7	28
Multigravida	67	24	3	94
Total	76	36	10	122
Percentage incidence	1.9%	0.9%	0.2%	3.0%

*In addition we have a smaller group of cases, 438, which have been excluded. These are emergency cases in which the patients have not received full obstetric care. In this group there were 24 patients with toxemia; mild 13, severe 6, and eclampsia 5. The incidence of toxemia for the combined groups is 3.3 per cent.

In the entire group of 4,004 patients, there were 122 patients with toxemia of pregnancy. These are shown in Table I. This classification based on the clinical evaluation of the patient in terms of blood pressure changes and the presence or absence of albuminuria, edema, and toxic symptoms. (Laboratory facilities for special diagnostic procedures were not available.) A systolic blood pressure of 140 was used as the starting point of toxic hypertension. Since most of the blood pressures were taken with a Tycos instrument, and by palpation, the records do not show the diastolic blood pressure. The observation of nephritic changes was limited to the presence or absence of albuminuria, as determined by the heat acid test. Needless to say, there are a number of possible combinations of these criteria.

The beginning and the termination of the toxic period was based on hypertension and albuminuria as reported on the records of the respective patients during the prenatal period. Puerperal blood pressures and urinary findings are not included, since they were not recorded for the entire group. Such findings were considered toxic if found on two or more consecutive prenatal visits. However, there were 6 patients

*Gross maternal mortality rate.

way below the adequate caloric intake, and many are on the borderline or below the usual vitamin requirements. The protein values are especially low, but most of the patients receive 10 per cent or more of their total calories from this type food. The diet is low in carbohydrate, but they do receive a generous supply of fat. The low vitamin intake, however, does afford protection against deficiency diseases. During the period of the author with the Service (nine years), there have been 3 obstetric patients with deficiency diseases (2 patients with pellagra, and a third with neuritis). It is significant that this dietary was obtained in the season of the year (early fall) when the supply of food available for consumption is more plentiful. It is also the season in which we found our lowest rate of toxemia. On the other hand, the greatest number of our toxic cases appeared in the winter-spring period, which is also the period in which the food supply is most restricted.

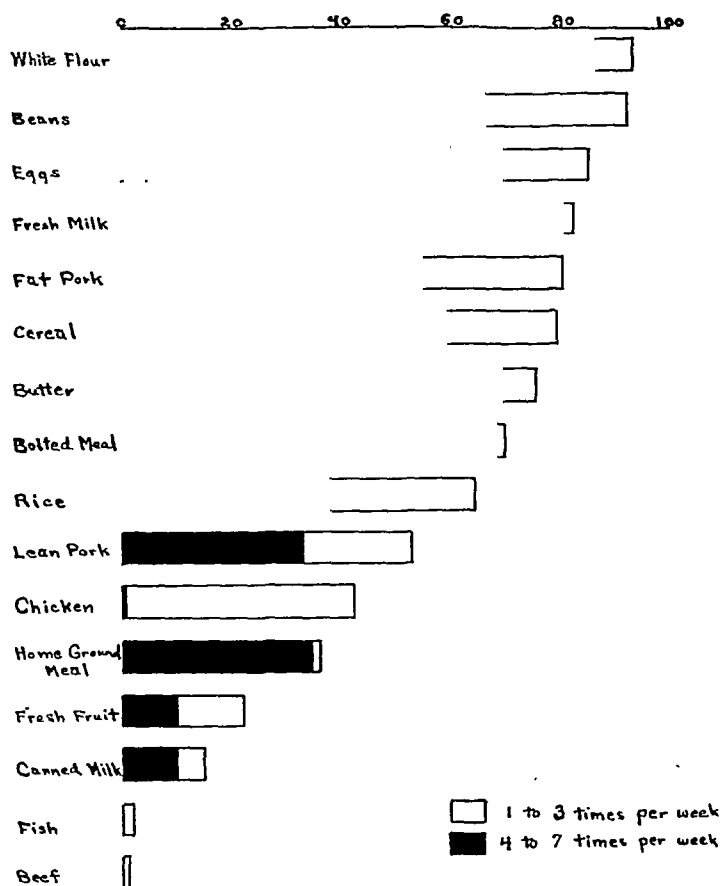


Chart 1.—Food habits of the rural group. Comparison of consumption of food items 1 to 3 days per week and 4 to 7 days per week by percentage of total families.

The toxemia rate reported shows a total incidence of late toxemia of pregnancy of 3 per cent, from a rural group of patients who have received adequate prenatal care. In this group only 10 patients (0.2 per cent) developed eclampsia. There were no maternal deaths due primarily to toxemia. (The one reported death occurred in the third week of the post-partum period from cardiorenal disease.) These

corresponding calendar weeks, it was found that 70 per cent of the cases appeared in the winter-spring season and 30 per cent appeared in the summer-fall season. Table II shows the incidence of the toxic cases in the four seasonal divisions. Dividing the total deliveries according to the seasonal distribution, we find: winter-spring, 2181; summer-fall, 1823; showing 54.5 per cent in the winter-spring period, and 45.5 per cent in the summer-fall period. It is evident that the seasonal variation in the incidence of toxemia cannot be accounted for by the variation in the total number of registered obstetric patients alone.

Table III shows the mortality incidence of the toxic group.

TABLE III. MORTALITY

	MILD	SEVERE	ECLAMPTIC	TOTAL
Total births	82	39	11	132
Full term stillbirths	2	1	2	5
Premature stillbirths	2	4	1	7
Neonatal deaths	0	1	0	1
Maternal deaths	0	1	0	1

There was a total of 132 births including 1 set of triplets, and 8 sets of twins. There was one anencephalic monster, and one macerated fetus. There were two non-viable fetuses of twenty-four weeks' gestation delivered of mothers with severe toxemia. There was one neonatal death, a premature infant who lived five days. There was one maternal death, that of a patient with severe toxemia who died on the seventeenth day of the puerperium from cardiorenal disease.

The foregoing obstetric analysis is of additional interest in view of the low income of the respective families. In this area the total income per family, including the cash value of crops, milk, meat from the cattle and the pigs, is \$364.00 per year.^{3, 4} As a direct result, the diet on which most of the people live is considerably less than that usually considered a minimal one for health.⁵ This was substantiated by a nutritional survey⁶ which was conducted in 1939 (February, March, April, May). Chart 1 shows the dietary of these families in the winter-spring period, as obtained from 330 families, 24 per cent of the total families carried by the Frontier Nursing Service, and indicates the frequency with which they consume available foods. Most of the foods consumed are produced locally. With poor soil for farming and with very low cash income, the diet is necessarily limited. However, it does afford a basic fare compatible with active life, and does protect against the usual deficiency diseases.

In addition, it was our good fortune to have a study made of the nutritive value of the diets of some of our obstetric patients. For this purpose, we had the services of an experienced nutritionist who personally conducted the survey. The survey was done in the fall period (September, 1939). The results are given in Table IV. Seventeen of the patients were in the last trimester of the prenatal period, while 3 were in the post-partum period. The entire group were normal obstetric patients.*

It is evident that this group of patients are living on minimal dietary requirements as compared with diets which have been generally considered as optimal for obstetric patients.⁷ A number of the patients are

*Patient 15 in the chart had had pellagra in the early part of her prenatal period, and was successfully treated with nicotinic acid.

findings appear to be low as compared with other available reports.⁸⁻¹⁰ Such reports, however, are from private practices, or from city clinics, and are not fully comparable since they represent urban or semi-urban individuals and do not indicate the toxic rate for an entire group (or population area). With surveys which were comparable, one could determine whether or not there were significant sectional differences in the amount of toxemia, and whether or not habits and modes of life were contributing factors.

CONCLUSIONS

1. The incidence of toxemia is reported from a rural group who have received complete obstetric care from the staff of the Frontier Nursing Service.

2. The incidence is reported in terms of the general types of toxemia and according to the season of the year in which they occur.

3. The diet studies of normal obstetric patients in this area are given. This indicates a low protein, low carbohydrate, high fat diet.

4. There does not seem to be any causative relationship between the incidence of toxemia reported and the current diet.

5. There appears to be a direct relation between the seasonal incidence of toxemia and the seasonal scarcity of food.

I wish to express my appreciation for the helpful advice given by Dr. Robert Lewis of Yale University, New Haven, Conn., and by Dr. M. Blankenhorn of the University of Cincinnati, Cincinnati, Ohio. I am indebted to Miss Jean Grant of the Medical Department of the University of Cincinnati, Cincinnati, Ohio, for the "Nutritive Diet" chart. Valuable assistance was rendered by Miss D. Buck, Assistant Director, and by Miss G. Weeks, Statistician, of the Frontier Nursing Service, Wendover, Ky.

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TABLE IV. THE NUTRITIVE VALUE OF THE DIETS OF TWENTY PREGNANT WOMEN

CASE	GM. P.	GM. F.	GM. C.	TOTAL CALORIES	MINERALS			VITAMINS			SIERRIAN BORQUIN UNITS G (RIBOFLAVIN)
					GM. Ca.	GM. P.	GM. Fe.	A	B ₁	C	
1	31	72	200	1,572	0.573	0.649	0.0048	1,371- 8,277	98	882-1,218	185-306
2	49	66	320	2,070	0.812	1.152	0.0094	2,778- 4,089	200	749-1,504	353-482
3	62	150	354	3,014	1.392	1.343	0.0137	3,006-28,109	263	937-1,881	711-786
4	73	106	436	2,990	1.465	1.830	0.0145	4,217-23,228	321	1,564-3,203	547-852
5	56	125	294	2,525	0.431	1.146	0.0696	2,232- 4,288	240	386- 738	149-149
6	44	54	385	2,202	0.232	0.995	0.0421	1,627- 3,469	194	1,052-1,588	147-220
7	39	95	354	2,427	0.248	0.571	0.0111	1,652-12,065	163	594-1,153	153-188
8	82	156	398	3,324	1.441	1.723	0.0254	2,421- 2,777	237	777-1,516	431-701
9	44	68	265	1,848	0.751	1.043	0.0065	1,686-10,716	194	772-1,369	270-413
10	70	95	258	2,167	0.234	1.648	0.0098	2,430- 5,428	238	283- 414	55- 75
11	37	69	167	1,437	0.530	0.811	0.0152	965- 2,340	189	433- 913	117-190
12	61	128	315	2,656	1.491	1.338	0.0126	3,029- 9,344	291	1,682-2,785	513-850
13	74	105	272	2,329	1.591	1.869	0.0138	2,681- 5,733	293	1,346-1,950	578-886
14	42	51	282	1,755	0.145	0.926	0.0099	477- 663	174	238- 370	62- 91
15**	39	81	261	2,019	0.595	0.703	0.0168	2,738- 5,716	117	485-1,056	163-276
16	64	88	394	2,642	0.715	0.977	0.0114	3,950- 7,999	244	783-1,364	186-266
17	41	106	247	2,106	0.383	0.761	0.0101	1,637- 3,950	184	448-1,062	107-145
18	45	56	214	1,540	0.262	0.774	0.0099	1,421- 4,891	162	358- 486	73- 96
19	45	69	217	1,669	0.415	0.736	0.0071	1,127- 2,991	139	383- 871	223-377
20	34	69	292	1,925	0.413	0.754	0.0080	1,781-19,802	209	648-1,089	224-305
Medians for the 20 patients	45	84.5	287	2,136.5	0.5515	0.986	0.01125	1,733- 5,572 4,168	197	698.5-1,185.5 698.5	185.5-290.5 235.75

Median age, 29 years; median weight, 137½ pounds

**The birth weights are available on 130 of the total deliveries. The range in the combined live and stillbirth weights is as follows: minimum, 12½ pounds; average, 7½ pounds; maximum, 12 pounds.

In the remaining 13 per cent, castration was planned because of debilitating extrapelvic lesions, such as carcinoma of the breast and advanced pulmonary tuberculosis.

The technique of administration and the dose of radiation required to produce castration* varies considerably in the reports of different authors.^{2, 3, 5-10} These reports also suggest that it is not common practice to vary the roentgen dose according to the size of the patient.

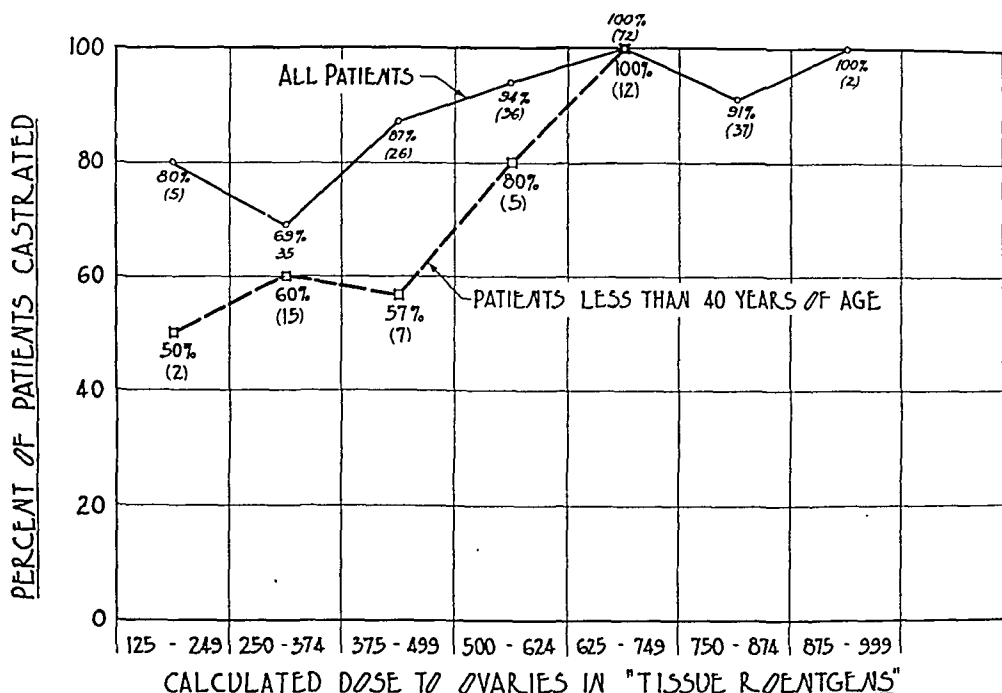


Fig. 1.—The efficiency of different roentgen ray doses delivered to the ovaries in producing permanent castration.

This fixed dosage was also used for many of the patients in this study early in the period covered by this report. In later years, this procedure was altered according to the patient's weight, and sufficient information was available in the records of 213 patients to calculate the roentgen dose to the ovaries. The depth dose and backscatter figures for water phantoms by Arenson and Quimby¹¹ and the isodose curves of Weatherwax¹² were used in this calculation. These cases were grouped according to computed ovarian dose and efficiency of castration as shown in Fig. 1. Any recurrence of uterine bleeding two or more months following irradiation and lasting more than one day was considered a failure of castration. This definition was adopted to exclude "spotting."

It should be noted that 5 of the 6 patients receiving the smallest amount of irradiation given in this series (125 r. to 249 r.) and intended as a temporary or subcastration dose were castrated permanently. As the dose of radiation increased, the percentage of patients castrated similarly increased. Since younger individuals (under 40

*The word castration is used for want of a better term to imply cessation of ovarian function responsible for menstruation rather than removal of the ovaries.

IRRADIATION OF BENIGN PELVIC LESIONS

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THE earliest record of an attempt to control uterine bleeding by irradiation in the University of Michigan Hospital was in 1904, only a few years after the discovery of x-rays. Since that time improvements in equipment and technique have been made which enable one to be fairly accurate in applying various doses of radiation. The use of radiation for this purpose, however, has not been generally accepted on the grounds that the menopausal symptoms produced were more severe than those associated with spontaneous menopause or surgical castration. Notwithstanding recent reports in the literature to the contrary, the opinion seems fairly widespread that the psychic changes observed after irradiation are much more pronounced than after the normal menopause, and that a frank psychosis or severe impairment of health may result.

The objectives of this study were: (1) to determine the efficiency of irradiation in the control of uterine bleeding, (2) to evaluate the menopausal symptoms which might ensue, and (3) to improve our method of applying roentgen radiation for the purpose of castration. A report by Kretzschmar and Gardiner of this Clinic concerning surgical menopause in hysterectomized patients will be used as a basis for comparison in evaluating menopausal symptoms.

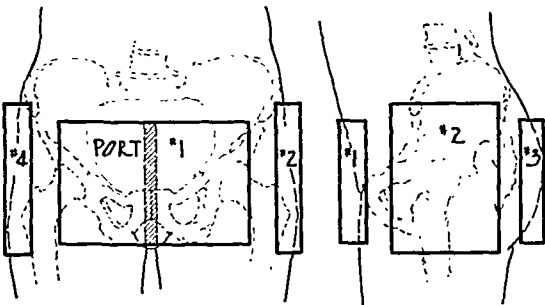
This report is based on the records of 334 patients treated with x-ray or radium for benign pelvic lesions. These patients received their treatment during the period July 1, 1925, to July 1, 1937, and the follow-up information was obtained by questionnaire or examination six or more months after treatment. Most of the patients were 40 years of age or older, only 45 of the 334 being in the younger group. The complaint on admittance in 260 (78 per cent) of the 334 patients was abnormal uterine bleeding. This included excessive or irregular bleeding at the menopause in patients without palpable changes, bleeding from uterine fibrosis or small fibromyomas and, in a few instances, excessive bleeding in young adults without demonstrable pelvic abnormalities which had failed to respond to conservative measures. All of these patients were curetted on one or more occasions, and material so obtained was examined carefully microscopically to rule out the presence of malignancy. A smaller group, 52 in number (15 per cent), had chronic pelvic inflammatory disease. Most of these patients had as one of their symptoms some abnormality of menstruation or had exacerbations of pelvic symptoms at the time of the period. The majority were individuals beyond forty years of age in whom surgery was not thought to be indicated. Endometriosis was present in 9 patients (3 per cent).

for castration in most instances. Attention is called to the one patient who received less than 500 mg. hr. and yet was permanently castrated. Here, as with x-ray in small doses given for temporary or partial castration effect, sufficient uncertainty exists to offer a serious objection to their use in young individuals with the hope that symptoms will be controlled without interference with fertility in later years.

There were no deaths following either x-ray or radium in this series. Two patients had a febrile reaction after treatment, one patient receiving x-ray and another radium. The cause of the fever was not apparent from clinical investigation but was assumed to be a mild exacerbation of a quiescent inflammatory process in the pelvis. Neither of these patients was acutely ill but represented a postirradiation febrile morbidity of 0.6 per cent.

FACTORS:

200 K.V. (Max), 0.50 MM. CU. + 2.00 MM. AL.
H.V.L. 0.80 MM. CU., T.S.D. 70.00 CM.
ANT. AND POST. PORTS 20 × 12 CM.
LATERAL PORTS 15 × 12 CM.



DO NOT EXCEED 250r TO EACH OF 2 PORTS PER DAY.

ANT.-POST., DIAMETER OF PELVIS (SYMPHYSES)

CM.	14	16	18	20	22	24	26
24	285	310	345	375	410	445	
26	300	330	365	400	435	480	525
28	315	345	385	425	465	515	570
30	330	365	405	455	500	560	615
32	345	385	435	480	540	610	675
34	360	405	460	515	580	660	740
36	375	422	480	545	620	710	800
38		440	505	580	660	765	870
40			530	610	695	815	945

Fig. 3.—Permanent castration by roentgen rays. Doses for various sized individuals, using anterior, posterior, and lateral ports. Total dose per port (measured in air without backscatter) required to deliver 625 "tissue roentgens" to the ovaries.

Among the 286 patients followed one or more years after castration, one patient developed carcinoma of the cervix (0.34 per cent) eleven and one-half years after castration by irradiation.

All of the 334 cases were included in evaluating clinical symptoms. They were divided into main groups: the castrated and the noncastrated according to the definition previously given. Each group was studied with regard to the two symptoms usually associated with the menopause; namely, hot flushes and change in sex life. No attempt was made to obtain information concerning the severity of the hot flushes, because as pointed out by Kretzschmar and Gardiner,¹⁵ such data are highly unreliable. Of the 160 patients who were castrated and were free from hot flushes before irradiation, 118 (73 per cent) developed this symptom following treatment. Furthermore, among the 32 patients not castrated, 62 per cent developed hot flushes. In the study of surgical castration, 86 per cent of the patients developed hot

years of age) were castrated in a smaller percentage of instances with similar doses, it appears that at least 625 r. to 749 r. to the ovary is necessary in order to assure permanent castration regardless of age (Fig. 1). Castration doses reported in the literature^{1, 5, 10, 16} have not indicated that such large amounts are necessary.

Some of the patients in this series received 600 to 1,000 roentgens (surface dose measured in air without backscatter) to each of two pelvic ports delivered within a few days. In a number of instances this caused temporary bladder, bowel, and skin irritation. In order to overcome this difficulty, a new technique of irradiation was devised. This method employs large anterior and posterior ports which are divided along the midline of the body by a 2 cm. strip of lead rubber, making in effect two anterior and two posterior ports centered approximately over the ovaries. By using in addition, two lateral ports, the necessary anterior and posterior skin dose can be reduced by approx-

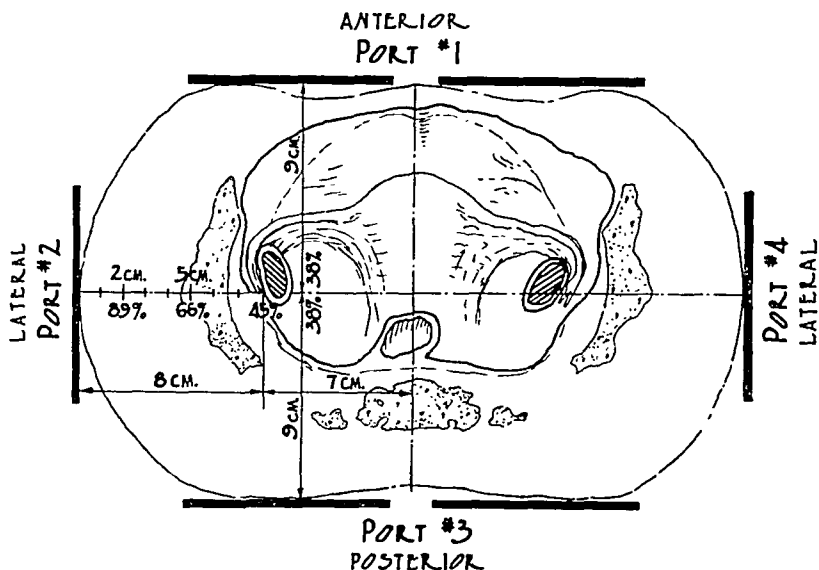


Fig. 2.—Method of calculating total depth dose in "tissue roentgens" delivered to each ovary. Cross section of female pelvis at level of symphysis pubis.

imately one-third (Fig. 2). Fig. 3 shows the size and location of the ports and the surface dose of radiation (measured in air without backscatter) which must be applied to each of the six ports to deliver 625 roentgens to the ovaries of patients with various pelvic measurements. Since using this method of application, a definite decrease in discomfort has been noted.

There were 58 patients treated by irradiation whose pelvic measurements were not recorded. These were not included in the previous charts but are included in the study of clinical symptoms.

Sixty-three patients were treated by means of an intrauterine application of radium. As shown in Fig. 4, 1,000 to 1,500 mg. hr. of radium (1.5 mm. platinum filter) were efficient in 77 per cent of the cases. While the group receiving more than this amount is too small to permit conclusions, it is probable that 1,500 to 2,000 mg. hr. should be sufficient

DISCUSSION

The use of radiation in adequate dosage, either x-ray or radium, appears to be an efficient means of controlling benign bleeding. It is most applicable in women approaching the menopausal age who have completed their reproductive activity. The age at which a patient should be considered as near the menopause is debatable but since reports on large series of cases indicate that the menopause occurs before forty years of age in 5 to 12 per cent of women, and between 40 and 45 in 75 per cent to 80 per cent of the women, a woman of 40 or over may be considered as approaching the menopause. In properly selected cases in this age group, radiation is preferred to hysterectomy because, (1) it has proved to be efficient, (2) it is practically without risk, and (3) it is much more economical. Furthermore repeated observation of these patients gives rise to the impression that the menopausal symptoms which develop are no more severe nor of longer duration than those associated with the normal menopause.

A diagnostic dilatation and curettage should always precede the treatment to avoid overlooking possible malignancy. In the presence of palpable disease of the adnexa, surgical intervention is preferable, since it permits adequate inspection of the pelvic lesion. Furthermore, we are of the opinion when fibromyomas are present which exceed the size of a two and one-half to three months' pregnancy that surgical removal is better than irradiation, because it completely eradicates the lesion, prevents recurrence of symptoms, and avoids complications due to degenerative changes in the tumor.

In young women, radiation should be used only when conservative measures fail or other methods of treatment are contraindicated, since castration by any method is to be avoided in this group whenever possible. Since the methods of temporary or subcastration seem so unreliable, we advise against the use of even small doses of radiation in these patients. If conservative measures fail in the treatment of abnormal bleeding in the young woman, it is felt that hysterectomy is to be preferred, since retention of the ovaries is definitely desirable for their psychic value, and also in the hope that they will retain their endocrine function. Radiation, however, should be used in these patients if they are poor operative risks.

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flushes after bilateral oophorectomy and 58 per cent developed them after hysterectomy with ovarian conservation. From this, one may conclude that the incidence of hot flushes after castration by irradiation is somewhat less than following bilateral oophorectomy. Furthermore, these figures (58 per cent and 62 per cent) suggest that subtotal hysterectomy with ovarian conservation will alter ovarian function to almost the same extent as incomplete castration by irradiation.

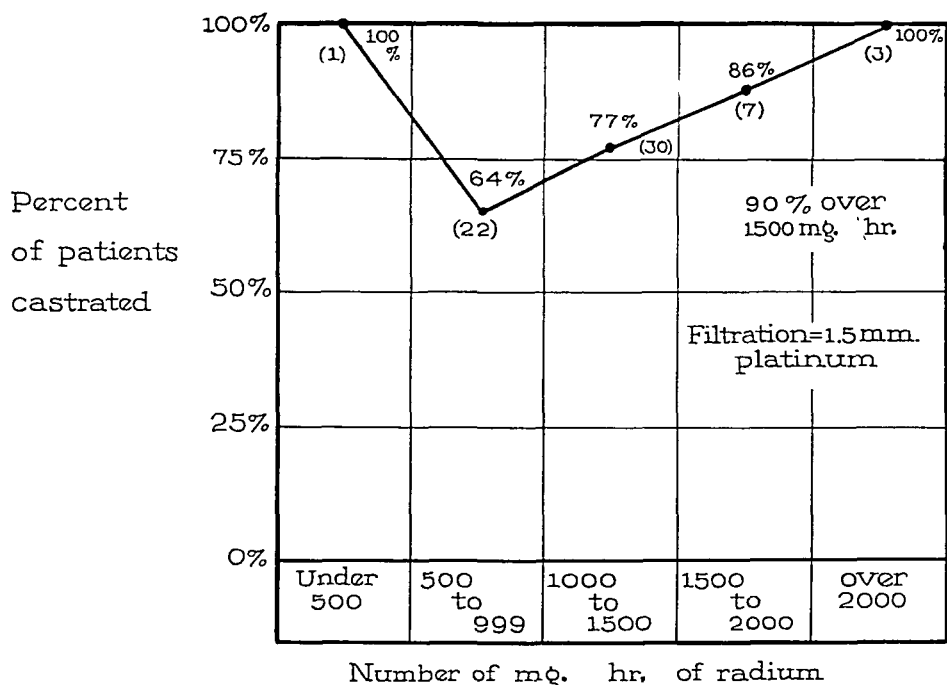


Fig. 4.—The efficiency of radium doses in producing permanent castration.

In many instances, the maintenance of sex life is of far greater importance to the patient than the presence or absence of menopausal symptoms. In order to permit accurate comparison, the wording of our questionnaire regarding libido was similar to that used by Kretschmar and Gardiner in their study of hysterectomized patients. In the 253 castrated women studied, 108, or 42 per cent, reported a decrease in libido, while 145, or 58 per cent, reported either no change or an increase. In the 63 patients who had a recurrence of menstruation, 23, or 36 per cent, stated that there was a decrease in libido. Comparing this with the effect of surgery, it is noted that the surgical and radiation effects are about the same. Since this group consisted of patients of all ages, an attempt was made to eliminate the factor of advancing years as a cause of decrease in libido by considering only patients under 40 years of age. In this group only 10, or 22 per cent, of the 45 women who were castrated noted a decrease in libido. From these figures it appears that both libido and hot flushes are to a certain extent independent of the ovarian secretions responsible for menstruation.

Although no figures concerning general health are available for comparison, it may be stated that there were no replies suggesting impairment of health, either mental or physical, and that there were many comments indicating a marked improvement.

canal and of the total depth of the cervix and uterus. All these patients had previously been classified as hypoplastic on admission and measured at the time of tubal insufflation.

Our criterion was not size alone, but the relative proportion of cervix to fundus, the presence or absence of a long supravaginal cervix, the shape and consistency of the fundus, and the shape as well as the size of the cervix.

Patients were rechecked and remeasured before beginning therapy and at frequent intervals thereafter. We measured the length of the cervix to the internal os and then the total length from the external os to the fundus, by means of a graduated sound. In the occasional case where we could find no clear-cut landmark of the internal os, we took only the total length as an indicator. These measurements were made at varying times in the menstrual cycle, and we found no difference in the measurements that could be attributed to the various menstrual phases. We especially did not notice any difference in the internal measurements of the premenstrual uterus versus the postmenstrual. We made no permanent record of any measurements that did not occur on two consecutive occasions. The majority were clinic patients but some were private. With one exception the total length of the cervico-uterine canal was $2\frac{1}{2}$ inches or less.

Symptoms were never inquired into specifically. All side effects and reactions from stilbestrol therapy were offered spontaneously by the patients. From time to time some of the patients were injected with sterile oil without their knowledge and invariably no symptoms were produced on those occasions.

The ages of these patients varied from 22 to 35 years, most of them being between 25 and 30.

They were of average weight, ranging from 120 to 150 pounds. None in the group was excessively thin or excessively overweight.

Result of Therapy.—In not one case did we see any improvement or other effects on the secondary sex characteristics. There was no enlargement of the breasts or labia. Three patients developed engorged, swollen, and painful breasts. Two of these were quite severe, the other only slightly so. One of these patients with oligomenorrhea had had some breast discomfort for many months. Her symptoms were aggravated and persisted for three months after cessation of therapy. In the others, the symptoms cleared up on discontinuing medication.

All breasts were frequently examined, and no patient developed any masses, glands, or other abnormal signs.

Effect on Menses.—Three of the 5 amenorrheic patients showed no effects whatever. One patient developed withdrawal bleeding. She showed a late proliferative endometrium prior to onset of therapy. She received 5 mg. of stilbestrol three times weekly for three weeks, at which time the dosage was reduced to 1 mg. because of the severe side effects, and a second endometrial biopsy taken at this time showed an atrophic endometrium. The fifth patient had had fifteen years of amenorrhea. She developed a profuse gushing, watery discharge per vagina which continued during ten of her fourteen weeks' treatment. She was subsequently curetted under anesthesia, at which time absolutely no endometrial tissue could be obtained even after vigorous efforts.

None of the 10 patients with oligomenorrhea showed any improvement.

Only 4 of the normally menstruating women did not experience some interruption in their menstrual cycle. In 7 of them, the menses were inhibited during administration of the drug and returned shortly after its discontinuance. These patients usually had accompanying nausea and urinary frequency, and as the uteri were enlarged at that time we stopped therapy on all and did Aschheim-Zondek tests on some of them. All of these were reported negative for pregnancy. Two of these patients passed pieces of membranous tissue with the returning menses. We did not do endometrial biopsies on this group during the period of amenorrhea because of the suspected possibility of pregnancy, and we were unable to do them after receipt of the negative reports, as in the meantime they had begun to menstruate shortly after cessation of therapy.

One patient developed menorrhagia and metrorrhagia after the third injection, and this continued until therapy was stopped. Two of the patients developed intermenstrual bleeding.

CLINICAL EVALUATION OF STILBESTROL IN WOMEN WITH HYPOPLASTIC GENITALIA

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THIS report deals primarily with the clinical experimental administration of stilbestrol in patients with hypoplasia of the uterus. The use of this drug was prompted by reports in the literature¹⁻⁴ ascribing to it the ability to cause uterine growth, although none of these papers gave satisfactory or conclusive evidence of its value in this respect.

As about 10 per cent of our sterility patients at Bellevue Hospital have definite hypoplastic and underdeveloped uteri one can readily see the value of any therapy that would produce uterine development. We are aware that uterine underdevelopment may be a sign of previous ovarian dysfunction and that it probably indicates concomitant ovarian hypoplasia. Nevertheless permanent uterine enlargement in some of these patients would eliminate at least one causative factor.

In our series 30 patients were given stilbestrol in oil, intramuscularly. With the exception of one menopausal patient all were sterile. There had been only one previous full-term pregnancy and one spontaneous abortion in the entire group.

Of the 30 patients, 28 had unmistakable hypoplastic uteri, among which 5 had secondary amenorrhea, 9 had oligomenorrhea, and 14 had normal menses. Two patients had normal-sized uteri; complaining of oligomenorrhea alone and the other of severe menopausal symptoms. In the entire series, 3 patients had menopausal symptoms.

Dosage.—The dosage of the drug used was 5 mg., three times weekly, except where severe side reactions compelled us to skip an occasional treatment or decrease it to 1 mg., three times weekly. This schedule was followed in all patients except 6. Three patients were started on 1 mg. injections and later increased to 5 mg., while 3 other patients were first given 5 mg. doses, and when they reacted too severely were changed over to 1 mg. injections. Side effects were present in all 6 cases but varied in intensity and number with the dose administered.

This dosage was arbitrarily chosen, some workers having used dosages varying from 1 mg. administered two or three times weekly to 10 and even 30 mg. daily. We were interested in giving a safe but adequate dose to eliminate the possibility of underdosage as a possible cause of failure in development.

Our patients received therapy from a minimum of two injections to a maximum of 42 injections over fourteen weeks. The patient with two injections received one at weekly intervals. She became so extremely sick with nausea, vomiting, and abdominal pain that therapy had to be discontinued. The patient with 42 injections had fifteen years of amenorrhea. She had some early nausea but apparently developed a tolerance to the drug. Her menses did not recur. The average duration of treatment was five weeks. The average number of injections was 15.

Selection of Patients.—In selecting our cases we were guided by our examination of the genitalia, cervix, and uterus, as well as actual measurement of the cervical

Robinson and Papanicolaou⁵ have attempted to throw light on this question by testing its effect on the liver by excretion studies, using both the hippuric acid excretion test and the intravenous bilirubin tolerance test. They compared their results with a series of control patients and also ran simultaneous urea excretion tests. Their results were so variable in both the control and the stilbestrol group that they were unable to draw any conclusion as to its effect on hepatic function.

MacBryde, Freeman and Loeffell, and Buxton and Engle⁹ followed a total of 54 patients, and their laboratory studies indicated an absence of any deleterious effect on the liver, kidney, or hematopoietic system in 53 of the patients. It may be interesting to note that MacBryde's series consisted of 12 patients with total ablation of the ovaries and 15 patients with severe spontaneous menopausal symptoms.

TABLE II. SIDE EFFECTS

	NONE	TOLERABLE	INTOLERABLE
Nausea	0	10	18
Vomiting	12	10	8
Anorexia	15	11	4
Headaches	8	8	4
Abdominal pains	11	17	2
Drowsiness and general malaise	22	0	8
Diarrhea	30	0	0
Vertigo	22	8	0

CONCLUSIONS

Except in rare instances this drug does not produce any demonstrable enlargement of the uterine cavity.

It seems definitely to have clinical estrogenic effects.

It produces undesirable side reactions in a large percentage of patients. These may or may not be toxic.

These side effects seem to be at least as frequent and as severe by the intramuscular route as those reported by the oral route.

These side effects are not permanent and disappear with cessation of therapy.

Its effect on the endometrium and on the menstrual cycle seems to resemble closely that of large doses of the natural estrogens.

Tolerance seems to be infrequently developed. There appear to be no cumulative effects from continued use of the drug.

In a small number of patients treated with varying dosages, it was our experience that the side effects varied with the dose administered.

The stilbestrol used in this study was furnished by E. R. Squibb and Sons, through the courtesy of Dr. J. A. Morrell.

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These menstrual effects clinically resemble those often obtained in cases of cystic and glandular hyperplasia of the endometrium.

TABLE I. EFFECT ON MENSES

	PATIENTS (5) WITH AMENORRHEA	PATIENTS (10) WITH OLIGOMENOR- RHEA	PATIENTS (14) WITH NORMAL MENSES
No change	3	10	4
Withdrawal bleeding	1	0	0
Menses inhibited	0	0	7
Menorrhagia and metror- rhagia	0	0	1
Intermenstrual bleeding	0	0	2
Serous discharge	1	0	0

Effects on the Uterus.—Of the 28 patients with hypoplastic uteri, only 5 showed either some temporary or permanent change in size or consistency of the uterus. These were all in the group of 7 normally menstruating women whose menstrual cycle was inhibited by the drug. Three of these were temporary and returned to the original condition on discontinuing the drug.

Two of the patients showed permanent changes. The first one showed a permanent increase of 1 inch in the cervical canal, the fundus remaining unchanged on palpation and measurement. This patient was under treatment for eight weeks, during which time she received 120 mg. of stilbestrol which is considered biologically equivalent to 1,500,000 international units of estrone.^{5 c}

The other patient received a total of 45 mg. in six weeks. She was so toxic that therapy had to be interrupted for one week. Her uterus increased in size from a total depth of 2½ inches to 3½ inches, the entire increase being confined to the fundus. This enlargement occurred in all diameters as confirmed by palpation.

Side Effects.—The marked discrepancy in the severity and importance of reported side effects is striking, despite the fact that by far the larger number of writers report unfavorable reactions. These differences do not seem to depend on the dosage or method of administration.

For example, while the earlier English writers reported favorable results with a minimum of uncomfortable reactions, Varangot,⁷ of France, simultaneously reported very severe gastrointestinal upsets in 8 out of 15 patients.

Very recently Shorr, Robinson and Papanicolaou reported 80 per cent severe reactions in a group of 44 patients, while MacBryde, Freedman and Loeffell,⁸ in a preliminary report on 37 patients, stated that in none of their patients was it necessary to withdraw treatment because of toxic manifestations.

In our series, therapy had to be stopped in 60 per cent of the patients because of the severity of the side effects. These consisted of nausea, vomiting, vertigo, headaches, general weakness, and lower abdominal pains in the order of their frequency. In the other cases, therapy was stopped because of interference with the normal menstrual cycle or because of no improvement. These reactions generally occur four to twelve hours after injection and last about twenty-four hours.

Only two patients (or 7 per cent) showed no side effects at all, but both experienced delay in the menstrual cycle. One of the amenorrheic patients began with severe nausea but developed a tolerance, and stilbestrol was discontinued after fourteen weeks because of no improvement. This and the menopausal patient were the only two developing a tolerance to the drug. This tolerance, however, was not complete but relative.

The cause and possible importance of these side effects remain to be determined. Whether they are simply uncomfortable side reactions or indicators of damage to the general body mechanism has not been decided and is still the subject of research. In our series, they certainly were clinically sufficiently severe and uncomfortable as to require extreme ingenuity on our part to convince the patients to continue as long as they did.

Their transitory nature and the fact that our patients showed no residual ill effects for as late as six months would suggest an irritative but nontoxic action. Shorr,

and is generally administered in 10 per cent aqueous solution, each 1 c.c. representing 0.1 Gm. of the crystals.

Our series of cases represents 53 unselected obstetric cases at the University Hospital, of which 38 were primiparas and 15 multiparas. All of them received evipal soluble in varying doses by rectal administration, and in conjunction all but 3 patients received scopolamine hydrobromide hypodermically.

ADMINISTRATION AND DOSAGE

The technique of administration of the drug was very simple. Three grams of the crystals were dissolved in 90 c.c. of tap water. To give 1 Gm., 30 c.c. of the solution were used. The patient was instructed to lie on her left side and an ordinary soft rubber catheter was inserted 4 or 5 inches into the rectum. The solution was allowed to run in by the force of gravity or, when necessary, a small "asepto" bulb syringe was used to introduce the solution. The buttocks were pressed together for a few minutes after the catheter was withdrawn and the patient told to retain the solution. The scopolamine was given hypodermically at about the same time as the evipal. An enema should be given some time prior to the instillation of the evipal. All patients in our series received an enema when admitted to the ward and did not receive one prior to the administration of the drug.

The criteria used in determining the proper time for administration of the evipal were, (1) when it was definitely ascertained that the patient was in true labor, (2) when she began to complain of pain and ask for relief, and (3) after the cervix showed effacement and 3 or more cm. dilatation.

In all cases, the initial dose of evipal was 1 Gm. If after one or two hours it was thought necessary, one-half the original dose or the entire original dose was repeated. This was done in only two of our cases.

EFFECT OF THE DRUG UPON THE MOTHER

The effects were found to be quite constant. Generally labor was not prolonged. In this series the average length of labor for the primiparas was fifteen and one-half hours, and for the multiparas twelve and one-half hours. One primipara was in labor sixty-two hours and forty-five minutes, the cause of the dystocia being a rigid cervix which ultimately required Dührssen's incisions and instrumental delivery of a stillborn child. This patient was given evipal soluble, 1 Gm. rectally and $\frac{1}{150}$ gr. of scopolamine hypodermically early in labor and this combination repeated forty hours prior to delivery. It is the only case in which the original dose of evipal soluble and scopolamine was repeated.

Generally, the drug did not stop pains if the patient was actually in labor. However, if it is given too early, i.e., before pains are well established and before effacement and dilatation of the cervix has begun, the patient may go to sleep and labor pains stop entirely. In one of our patients the pains stopped and she went to sleep soon after the drug was administered. The next day labor started again, but this time the drug did not affect the pains and the patient delivered uneventfully following a normal labor.

The time between the administration and actual delivery varied a great deal. The longest time was forty hours and the shortest twenty-nine minutes. In none of these cases were there any ill effects noted

THE USE OF EVIPAL SOLUBLE RECTALLY IN OBSTETRICS*

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VARIOUS drugs and combinations of drugs have been resorted to for analgesia and amnesia during labor, since the memorable work of Steinbüchel and Gauss⁸ in introducing scopolamine and morphine as the means of alleviating pain during the process of labor. In most clinics in this country, the original "twilight sleep" has been abandoned, because it was found so often to lengthen the process of labor, to cause a high percentage of operative deliveries, and in a large number of cases to produce fetal asphyxia. Morphine seemed to be the most objectionable of the two drug components, also the repeated administration of scopolamine added another undesirable factor. In the search for something better than morphine, various compounds of barbituric acid have been used, either singly or in combination with scopolamine, with more or less success.

At present, the ideal analgesic and amnesic for labor has not been found. There is still controversy in the profession over the ill effects suffered by both the mother and the child from the promiscuous administration of analgesics and hypnotics. This should raise a question as to the value of information given by overzealous individuals in the daily press, magazine articles, and medical commentators on the radio which has often taught the laity to expect or demand too much alleviation from pain during parturition.

Evipal was first used, intravenously, for surgical procedures, requiring twenty to twenty-five minutes for completion. Weber¹ reports that in European clinics over 800,000 patients have received evipal intravenously with but four deaths directly attributable to the drug. This same author also reported on its use intravenously in obstetrics but stated that, because of its short period of anesthesia, it could only be used near the end of the second stage of labor and for that reason it proved to be inadequate.

Gwathmey,² in 1936, first reported the use of evipal soluble per rectum, and found it to be a safe and satisfactory means of basal anesthesia. He further stated that the technique was simple and easier to use than ether-in-oil per rectum and that no contraindications to its use were found.

Evipal soluble in obstetrics, by rectal administration, was first reported by Siegler and Beris³ in 1938. They showed in their 72 cases that this drug was a simple and safe analgesic and amnesic in obstetrics and that there were no deleterious effects on either the mother or the infant.

Evipal soluble is the sodium salt of evipal, known chemically as N methyl-cyclohexenylmethyl barbituric acid. It dissolves readily in water

*The evipal soluble used in this study was furnished through the courtesy of The Winthrop Chemical Company.

these responded readily to artificial stimulation. In each of these the medication was given five, four, and three hours, respectively, before the time of delivery. No drowsiness was noted after the babies were taken to the nursery. All of them acted quite normally and gave no further concern.

TABLE II

Babies with spontaneous cry	49	92.4%
Babies with delayed cry	3	5.7%
Stillbirth	1	1.9%

DISCUSSION

This series represents 38 primiparas and 15 multiparas to whom evipal soluble was given in hopes of producing analgesia and amnesia during parturition.

The effects upon the mother were quite gratifying. The average length of labor was not prolonged, in fact, the primiparous labors were somewhat shorter than the average. Labor pains did not seem to be diminished in intensity as is often seen with some of the other barbiturates.

It was our experience that all but one patient required some supplementary anesthesia during actual delivery. This is at variance with the results of Siegler and Beris³ who report 77 per cent of their patients not needing additional anesthesia. Their original dosage was larger than ours.

Since patients vary considerably in regard to their reaction to analgesics, it is difficult to state the correct dosage, much the same as it is difficult to state the exact amount of ether necessary to produce anesthesia. In our opinion, it was preferable to begin with 1 Gm. per rectum and repeat when necessary. We believe our results would have been better if the drug had been repeated in a larger number of the cases.

No untoward reactions were noted in this series, such as the convulsions during delivery as reported by Rosenblum and Webb.⁴

It was our routine, with but 3 exceptions, to give $\frac{1}{150}$ gr. of scopolamine hydrobromide at the time of rectal administration. We are quite sure that this greatly enhances the amnesic action of the drug. In no case, as admonished by Gwathmey² was any other barbiturate used in association with or prior to evipal soluble.

It is well to remember that the action of evipal soluble may be reversed by the administration of metrazol if the emergency should arise. This was used with good results in one of our patients, as already stated, who became too drowsy to deliver the baby.

No toxemias were observed in this series. Inasmuch as evipal soluble is detoxified in the liver, as stated by Jones,⁵ it would seem inadvisable to consider its use in any toxic case because of placing an additional strain on an already hampered organ.

No excessive uterine bleeding was encountered. Blood pressure determinations were not taken, because it has been amply shown by numerous investigators (Petersen,⁶ McNelis⁷) that no significant change takes place in this respect.

on either the mother or the child. The average length of analgesia was roughly $5\frac{1}{2}$ hours. The length of time required for the onset of analgesia after the administration of the drug averaged about fifteen minutes. At times this was somewhat difficult to determine because the patients were usually awake and responded well although they were often somewhat restless. At no time did any patient become wild or hard to manage. While this series was being run several other patients were given nembutal for analgesia. It was notable that the patients who had received evipal were quieter and more easily managed.

In 3 cases evipal soluble was given without the addition of scopolamine. The results in two cases were very interesting in that they obtained almost complete analgesia without amnesia. All patients were questioned twenty-four hours following delivery. The results classed as good, fair, and poor are shown in Table I.

TABLE I

Analgesia	
Good	36 cases 69%
Fair	10 cases 17%
Poor	7 cases 14%
Amnesia	
Good	32 cases 61%
Fair	8 cases 15%
Poor	13 cases 24%

None of the patients showed the evidences of proctitis that are sometimes seen when drugs are administered rectally.

ANESTHESIA USED FOR DELIVERY

In one primigravida, the entire delivery was accomplished with perfect analgesia and amnesia under 1 Gm. of evipal soluble and $\frac{1}{150}$ gr. of scopolamine given two hours before delivery. At the time of delivery, this patient was drowsy and unresponsive until 1 c.c. of metrazol was given intramuscularly, after which delivery was accomplished spontaneously. The baby cried immediately upon being born.

Another primigravida was delivered with the aid of $\frac{1}{2}$ per cent novocaine, using pudendal block anesthesia. One multipara was given cyclopropane with excellent results. The remainder of the patients received open drop ether at the time of delivery.

EFFECT ON THE BABY

All presentations were vertices except one which was a complete breech. There was one stillbirth which was caused by prolonged labor. The drug can hardly be blamed for the death of the fetus, as the patient was in labor over sixty-two hours, and the last dose of evipal was given forty hours prior to delivery.

There were no gross fetal ill effects encountered in giving the medication even when administered near the end of labor. In one case it was given twenty-nine minutes before the delivery.

No fetal asphyxia was encountered. All live babies cried spontaneously except three in which the cry was somewhat delayed, and

TABLE I. AGE DISTRIBUTION

AGE GROUP	CERVIX	CORPUS
0-9	4	
10-19	6	
20-29	7	
30-39	9	3
40-49	6	9
50-59	3	31
60-69	1	14
70-89		1
Totals	36	58

In the latter group, practically all occur after the menopause, whereas the majority of cervical tumors appear during active menstrual life. Parity exerts no influence on the etiology.

Most authors state that the cervix is the site of predilection, but careful search through the literature reveals 58 cases involving the corpus and only 36 in the cervix, a ratio of 1.6 to 1.

Eight cases have been associated with fibroids. In 6, the mixed tumor arose from the body, while in the remaining 2, the neoplasm was cervical in location. Cox and Benischek¹² reported such a tumor complicating pregnancy, and Reeb and Oberlings⁸¹ described one coexisting with a carcinomatous polyp of the fundus.

GROSS APPEARANCE

Cervical tumors usually arise from a narrow pedicle and are grapelike and arborescent, although Jones'³⁷ case had an annular attachment about the external os. Tumors of the body appear as multiple polyps involving the anterior or posterior fundal walls. Both forms, however, can develop in either site.

On cross section, the tumors reveal cystic cavities intermingled with areas of hemorrhage, necrosis, and suppuration. Cartilage is rarely noted in the gross.⁷³

HISTOLOGIC APPEARANCE

These neoplasms are comprised of many elements foreign to the uterus (Table II).

TABLE II. HISTOLOGIC ELEMENTS

	CERVIX		CORPUS	
	NUMBER	PER CENT	NUMBER	PER CENT
"Myxomatous tissue"	27	75.0	41	70.7
Cartilage	20	55.6	35	60.3
Striated muscle	11	30.6	24	41.4
Smooth muscle	7	19.4	20	34.5
Rhabdomyoblasts	2	5.6	8	13.8
Glandular elements	6	13.9	33	56.9
Bone	3	8.3	3	5.2
Osteoid tissue	0	0	4	6.9
Fat	1	2.8	6	10.3
Stroma:				
Spindle cells	27	75.0	55	94.8
Round cells	22	61.1	22	37.9
Giant cells	5	14.0	19	32.8
Associated fibroids	2	5.6	6	10.3

The most common tissue is a loose, myxomatous-appearing stroma which many believe to be embryonal mesenchymal tissue, the anlage for all the other elements. Others contend that it is myxomatous in character, while still others feel that it is mucinous. Its microscopic structure is characteristic: triangular or star-shaped cells with long axionic strands connect with other cells to form a loose network. Their nuclei are either round or oval and usually single.

The results upon the baby were most gratifying. No cyanosis was encountered. The majority cried spontaneously, and only a small percentage needed artificial skin stimulation to initiate respiration.

CONCLUSIONS

1. In our hands, evipal soluble was a safe and effective analgesic and amnesic when given per rectum during labor.
2. Scopolamine hydrobromide hypodermically greatly enhances the amnesic effect of evipal.
3. When evipal soluble and scopolamine are given during labor, patients do not become as wild and unmanageable as is often seen when other barbiturates are given.
4. Evipal soluble is sufficiently satisfactory to deserve further study in a larger series of cases.

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A REVIEW OF NINETY-FOUR MIXED MESODERMAL TUMORS OF THE UTERUS*

WITH REPORT OF AN ADDITIONAL CASE

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MIXED mesodermal tumors of the uterus are rare and deserve a detailed study. A case of this type was observed at the Kings County Hospital and served as the basis of this study. Such tumors are defined as monodermal in origin, develop from mesoderm and consist of heterotopic and highly malignant tissues. Thus they differ from true teratomas which are of tridermal origin.

HISTORY

Ninety-four cases have been recorded to date. In 1854, Wagner¹⁰³ described the first case, but Thiede,¹⁰⁰ in 1877, was the first to emphasize the presence of cartilage and a myxomatous stroma. In 1892, Pfannenstiel⁷⁴ recommended calling such tumors "traubiges Sarkom" or botryoid sarcoma, a term still in common usage. Wilms¹⁰⁸ (1899) called them "mixed tumors."

CLINICAL FEATURES

In considering the age incidence, one must differentiate between cervical and corporeal growths (Table I).

*Read at a meeting of the Brooklyn Gynecological Society, October 4, 1940.

TABLE IV. TREATMENT

	CERVIX		CORPUS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total hysterectomy	15	41.7	39	67.2
Vaginal hysterectomy	1	2.8	1	1.7
Supravaginal hysterectomy	0	0	2	3.4
Dilatation and curettage	2	5.6	7	12.1
Amputation of cervix	5	14.0	0	0
Local removal	19	52.8	8	13.8
X-ray therapy	6	13.9	6	10.3
Radium	3	8.3	0	0

These neoplasms are malignant out of all proportion to their histologic appearance evidenced by the high mortality (90 per cent) regardless of therapy (Table IV). The average duration of life following removal is one year. Local recurrences are frequent. Cartilage indicates a highly malignant growth, whereas the presence of fat denotes a more benign one.¹⁵ The longest period of survival was recorded by von Franque:²⁰ The patient was living and symptom-free ten years postoperatively. Hartfall³⁰ cites a five-year cure.

CASE REPORT

B. G., a 50-year-old, widowed, nulliparous white woman entered the Kings County Hospital on the service of Dr. Charles A. Gordon on July 18, 1940, complaining of irregular vaginal bleeding for eight weeks associated with an offensive brown discharge for four weeks. The menopause occurred eight years previously. There had been no pain or weight loss. Her past personal and family history were essentially negative. On examination, the patient was well nourished, well developed and had a temperature of 101° F. The head, neck, and lungs were negative. The heart was not enlarged. A short, low-pitched murmur was heard over the pulmonic area. The abdomen was moderately tender throughout and contained a large, firm, movable mass arising from the pelvis. This filled the entire right lower quadrant up to a point three fingerbreadths below the costal margin. Pelvic examination revealed a brown, foul-smelling purulent discharge. The cervix was tender to palpation and admitted one finger. The mass described above, filled the pelvis but a detailed examination could not be carried out because of the pain produced by manipulation. *Laboratory data:* The urine was negative. The white blood cells numbered 11,800 with 82 per cent polymorphonuclear leucocytes and 18 per cent lymphocytes. The red cell count was 3.7 million and the hemoglobin 65 per cent. The sedimentation time was seventy minutes. The clinical impression was "carcinoma of the corpus with infection or septic missed abortion." The latter diagnosis was considered because, on admission, the patient had stated her age as forty years. She was treated as a missed abortion and given 20 gr. of sulfanilamide every four hours for five days. Following this, her temperature and white count fell to normal. Three transfusions totaling 1,100 c.c. were given to overcome the anemia. Two unsuccessful attempts were made to empty the uterus with pituitrin. Six days after admission, on July 29, a curettage yielded considerable tissue, diagnosed microscopically as a mixed mesodermal tumor. On August 15, thirty days after admission, laparotomy revealed the uterus enlarged to the size of a four and one-half months' gestation and the seat of multiple fibroids. A total hysterectomy with bilateral salpingo-oophorectomy was performed. Her recovery was uneventful, and she was discharged from the hospital twenty-one days later. At present, the patient is receiving deep x-ray therapy.

PATHOLOGIC REPORT

Macroscopic.—The specimen consisted of a uterus, practically all the cervix, both tubes and ovaries.

The uterus measured 12 cm. from the top of the fundus to the plane of trans-section, 11 cm. transversely at the level of the round ligaments, and 8 cm. in the anteroposterior diameter. The surface was nodular due to numerous, firm, sessile

The second most frequent tissue is hyaline cartilage. It occurs as small islands surrounded with a "perichondrium" of spindle cells. Transition of these cells to cartilage has been noted.⁶⁵

Striated muscle has been noted in 35 of the cases. However, these elements may have escaped notice, since they are sometimes found only after prolonged search and the use of special stains to demonstrate striations. Shapiro and others described large multinucleated cells which they believe are rhabdomyoblasts.

Bone and fat are uncommon. The former has been recorded in 10 cases, while the latter has been observed in only 7.

Most authors describe a pleomorphic sarcomatous stroma, consisting of round or spindle cells intermingled with multinucleated giant cells.

These tumors are extremely vascular. Hemorrhages are common and arise from the thin-walled capillaries.

The neoplasms are always submucosal in location. The overlying epithelium of corporeal growths is columnar in type while those in the cervix are covered with squamous or transitional cells. Should the lining be lacking, local pressure and necrosis are responsible. The surface epithelium rapidly proliferates to form gland spaces, adenomas, and solid cords of cells within the stroma. Cervical and endometrial glands have been observed.

Though nerve tissue and smooth muscle have been described, neither is heterologous to the uterus and consequently cannot properly be considered part of these neoplasms.

As a rule, the tumor is sharply demarcated from the myometrium. Where invasion occurs, it is associated with a sarcomatous-like stroma. In one instance myxomatous tissue penetrated the myometrium.

Metastases are common (Table III) though usually the patients die from operative complications or from cachexia and its associated phenomena.

TABLE III. METASTASES

	CERVIX		CORPUS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total metastases	26	72.2	35	60.3
Pelvis	12	33.3	12	20.7
Abdomen	8	22.2	20	34.5
Lungs and pleurae	3	8.3	8	13.8
Bones	0	0	3	5.2
Inguinal lymph nodes	1	2.8	1	1.7
Local recurrences	18	50.0	16	27.6

Infiltration into the adjoining viscera, such as parametria, bladder, vagina, and peritoneum, is frequent. Nicholson⁶⁵ describes the only case with ovarian metastases. The lungs and pleurae are frequent sites for secondary growths. Here they rarely reproduce the parent tumor but, instead, develop as a spindle cell or myxosarcoma. Cartilage has been observed to metastasize three times^{30, 31, 61} and striated muscle once.³⁴

HISTOGENESIS

The etiology of these tumors is unknown. Wilms' theory of displaced myotome and sclerotome elements is given most credence. He presumes that these structures are included in the Müllerian ducts, as they pass beneath the Wolffian ducts fusing in the midline to form the uterus and vagina. This is substantiated by finding mixed tumors in the base of the bladder, a "site of embryonic organoid tissue fusion and tissue amalgamation"² and by the absence of such neoplasms along the Fallopian tubes. The nature of the stimulus to growth is also unknown, but it has been predicated as hormonal.

DIAGNOSIS AND PROGNOSIS

The symptom caused by these tumors is: irregular vaginal bleeding associated with a sanguinopurulent discharge. Pressure symptoms occur if the mass is large or if the tumor has invaded surrounding structures.

was filled with large, irregular, yellowish white, friable polyps attached to the wall by broad bases which in places penetrated the muscularis up to the serosa. Section through the polyps revealed a homogeneous silvery white matrix, containing small bony or cartilaginous spicules. The myometrium was thin and contained numerous small fibromyomas.

Microscopic.—From the endometrial surface arose many large and small polyps covered with epithelium comprised, in the main, of a single layer of tall cells similar in size, shape, and staining intensity. They contained moderate cytoplasm and a large oval nucleus occupying the basal third (Fig. 2). Focal hyperplasia had occurred, and here they appeared three or four layers deep. In places, the surface epithelium penetrated the stroma to produce varying sized glands lined

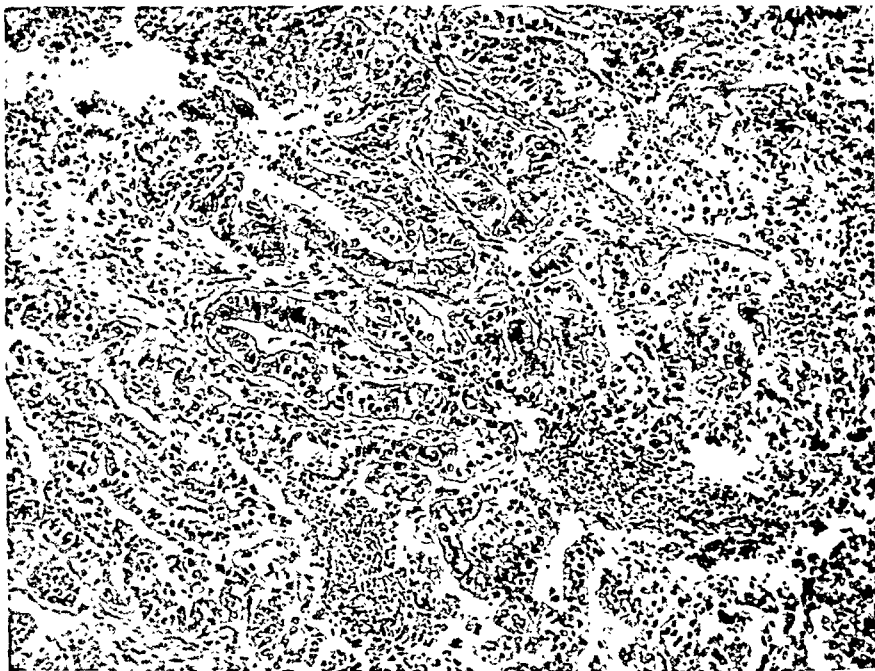


Fig. 3.—The section demonstrates the adenomatoid hyperplasia. The glands are profuse and vary in size and shape. Their lining cells are proliferating rapidly to form papillae which fuse with contiguous ones, producing daughter glands. Many cells and nuclei vary in size, shape, and staining intensity.

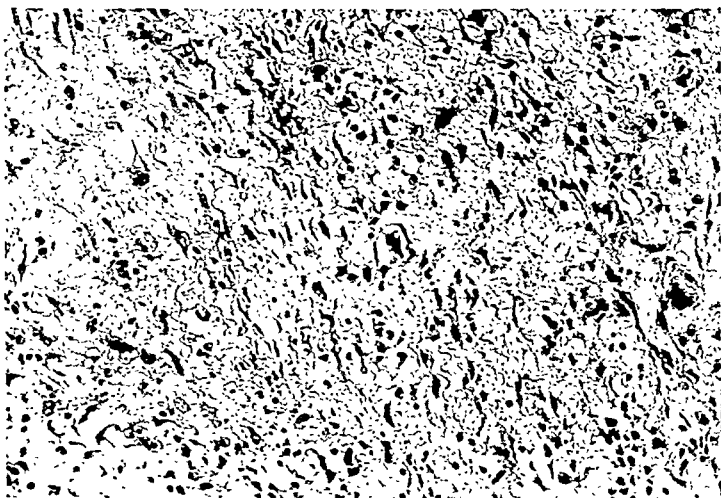


Fig. 4.—The stroma is mesenchymal in nature and comprised of triangular or star-shaped cells from which thin, long axionic processes arise and intermingle with each other.

and pedunculated tumors which varied from 1 to 9 cm. in diameter. On section, all the tumors presented the silvery whorls characteristic of fibromyomas and some of the larger ones revealed small areas of liquefaction necrosis. The segment of cervix measured 3 cm. long. The epithelium of the portio was lacking. The endocervical canal was dilated and lined with a smooth, thin mucosa. Its fibromuscular wall was compressed. On opening the uterus (Fig. 1), the cavity



Fig. 1.—The uterus contains many subserous and intramural fibroids. The cavity is filled with varying sized, homogeneous, gray white polyps that are focally hemorrhagic. On the right lateral wall, the tumor is tuberos in character and has invaded the myometrium.



Fig. 2.—The surface presents as small and large polyps covered with tall columnar epithelium. In places, the lining cells are growing down into the stroma and here form glands.

COMMENT

This case is reported because fibroids occur infrequently with mixed mesodermal tumors. Only 8 have been described previously. The clinical findings are in accord with similar cases as to age, symptomatology, and macroscopic appearance. The microscopic findings agree with the description of other observers. Muscle tissue could not be demonstrated despite the use of special stains as recommended by Glynn and Blair Bell.²⁸

No further elucidation of obscure points of histogenesis or therapy can be offered. Radical surgery followed by deep x-ray treatments should prove to be the best therapy, provided early diagnosis is established.

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with anaplastic cells. Papillation and sacculcation resulted in the formation of many daughter glands (Fig. 3). The stroma presented a varied picture. In some portions it consisted of compactly arranged small and large oval or spindle cells. In other areas a loose myxomatous matrix was the supporting tissue whose component cell was triangular or star-shaped and connected to each other by long axionic processes (Fig. 4). Multinucleated giant cells rich in chromatin were scattered about (Fig. 5). Parts of the stroma were necrotic and overrun with polymorphonuclear leucocytes. Islands of hyaline cartilage surrounded with a zone of spindle cells formed a "perichondrium" in other sites (Fig. 6). The

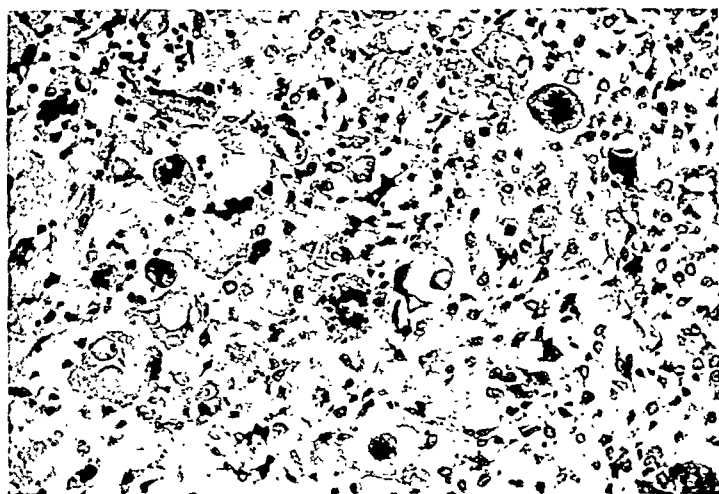


Fig. 5.—In the loose, gray white, embryonal, connective tissue matrix are seen many giant cells. Their nuclei are huge or multiple and rich in chromatin.

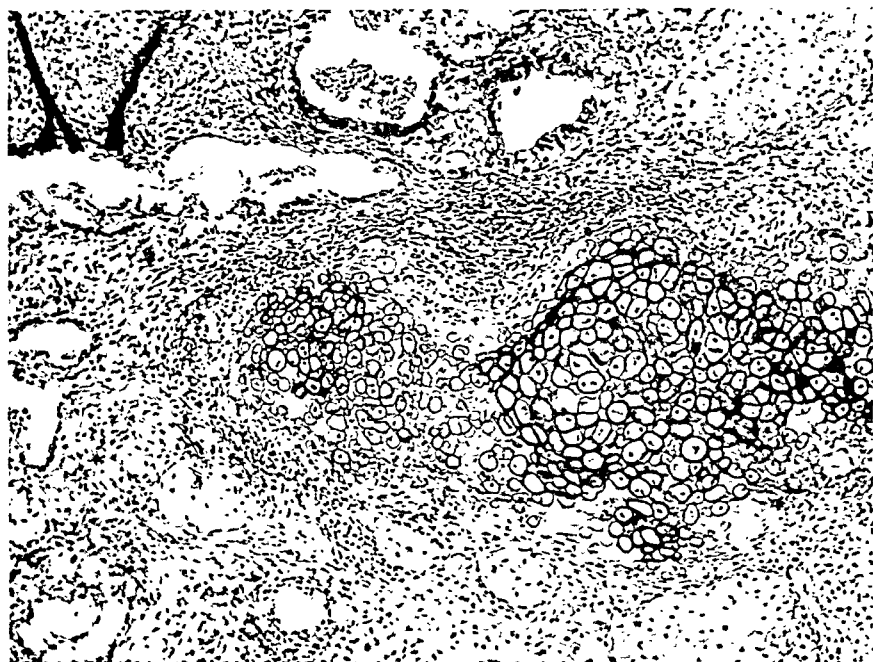


Fig. 6.—Islands of hyaline cartilage surrounded by a compact zone of spindle cells (perichondrium) are seen in the stroma.

myometrium was compressed and contained several encapsulated fibroids presenting hyaline degeneration.

In both tubes and ovaries, an intense inflammatory reaction was seen. No tumor tissue was encountered in any of these organs.

On admission to the hospital the temperature was 98.4° F.; the pulse rate was 84 and the respirations 20 per minute. The weight was 131 pounds and the height 59 inches. The patient did not appear ill. The organs of the head and neck were essentially normal except that the trachea deviated slightly to the right of the midline. The breasts were enlarged. The chest was symmetrical, but there was a slight delay in expansion of the left side of the thorax. The percussion note was dull over the left lower half of the chest and breath sounds were absent, while the sounds were accentuated over the right side of the thorax. Peristaltic movements were not heard. The rate and rhythm of the heart were normal and there was no pulse deficit. The blood pressure was 125 mm. of mercury systolic and 85 mm. diastolic. The right border of the heart extended to the right midclavicular line, while the location of the left border could not be determined. The uterus reached to within two inches of the xiphoid process, the fetal heart sounds were audible and the fetal head was engaged in the pelvis. Pelvic measurements were normal with an external conjugate diameter of 18.5 cm. and a bischial diameter of 10.5 cm. Rectal examination showed the cervix closed but partially effaced, and the coccyx was movable. There was moderate pitting edema of the ankles and the reflexes were physiologic.

Laboratory Examination.—The hemoglobin was nine grams (Haden-Hausser) per 100 cubic centimeters and the blood Wassermann and Kline reactions were negative. A sample of urine was not available.

Course in Hospital.—On December 10, at 8:00 P.M., the patient complained of pain in the epigastrium and discomfort in the lower part of the abdomen. It was evident that labor had begun since there was progressive dilatation of the cervix and a bloody "show." During the night uterine contractions continued at five- to six-minute intervals. The patient slept fairly well after being given gr. iii of pentobarbital sodium, but at 8:00 A.M., December 11, some dyspnea associated with moderate pallor of the skin developed. During the next two hours there was increasing cyanosis, orthopnea, dyspnea, and grunting expirations. The pain in the epigastrium became accentuated and radiated to the left lower chest. Fluoroscopic examination at 10:30 A.M. revealed a dextrocardia and what appeared to be stomach and small and large intestines above the diaphragm in the left side of the thorax. A small amount of barium given by mouth disappeared from the esophagus below the diaphragm and then reappeared above the diaphragm to the left of the esophagus, in what was believed to be the lower end of the stomach. Epigastric pain was now severe enough to require morphine. A duodenal tube was inserted into the stomach and approximately two quarts of air aspirated, without relieving the epigastric and left thoracic tympany which had been present since 9:00 A.M. By 12:00 NOON the administration of intranasal oxygen was required to relieve the respiratory difficulty. The patient died suddenly at 12:45 P.M., December 11.

Fetal heart sounds had not been heard for twenty minutes before the mother died. At the time of death the cervix was dilated 7 cm. and the bag of waters was intact. The membranes were ruptured, an incision was made in the anterior lip of the cervix, forceps were applied to the baby in L.O.A., and a normal-appearing stillborn female infant, weighing 3,260 Gm. was extracted.

Autopsy of Mother.—The body was that of a normally developed, well-nourished, white female. The head, extremities, and external surface of the body were not abnormal in appearance except for the presence of one accessory nipple on each side.

The abdomen was distended, tympanitic, and air escaped when the peritoneum was opened. Gross relations in the abdomen were greatly disturbed. The diaphragm on the right side was at the level of the fourth intercostal space, but on the left the dome was inverted and pushed down into the abdomen, so that it was 2 cm. below and parallel to the inferior rib margin.

The liver was crowded to the right. There were two distended loops of jejunum in the epigastrium, floating in 300 c.c. of blood and food particles. The spleen, which was enlarged to 430 Gm., was twisted one turn on its pedicle and lay just to the left of the midline.

When the left side of the thorax was opened, the taut, inverted left diaphragm relaxed. The left pleural cavity contained 450 c.c. of nonsanguineous fluid and food particles, together with a large portion of the stomach, most of the jejunum, all of

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142 JORALEMON STREET
855 PARK PLACE

DIAPHRAGMATIC HERNIA ASSOCIATED WITH PREGNANCY

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DIAPHRAGMATIC hernia producing complications among pregnant women is so uncommon that there are relatively few recorded cases. The patient here reported died during the first stage of her fourth labor from strangulation of the viscera in a diaphragmatic hernia. The case is also unusual in that there had been three previous uneventful deliveries, two of which had occurred after the diaphragmatic hernia had been discovered during laparotomy.

Case History.—G. S. (No. 39-16065), a 23-year-old housewife, gravida iv, para iii, was admitted to the University Hospitals Dec. 10, 1939, at 4:00 P.M. and died at 12:45 P.M. Dec. 11, 1939.

This patient, from 1936 to 1938, had delivered spontaneously three times, each baby weighing from 6 to 7 pounds. The labors were from two to three hours in duration and uncomplicated.

The menstrual history was normal. The last menstrual period began on March 12, 1939, and the expected date of delivery was Dec. 19, 1939.

The patient had been aware of a cardiac impulse in the right side of the chest for several years. An exploratory laparotomy was performed in January, 1937, for "appendicitis." The surgeon was unable to find the appendix and subsequently obtained a roentgenogram of the colon after a barium enema which showed loops of bowel in the left side of the chest.

a patent foramen ovale, was rotated counterclockwise, so that the right auricular appendage was posterior to the remainder of the organ. The almost completely atelectatic left lung lay on and just to the left of the midline, and weighed 140 Gm. There was a long, dense, fibrous adhesion between the base of this lung and the omentum, which was in the left side of the thorax. The right lung was compressed and lay posterior to the heart and other mediastinal structures. It weighed 300 Gm. and was partially atelectatic, especially in the lower lobe.

Examination of the remainder of the abdomen and the pelvis revealed the following: The pancreas, which weighed 100 Gm., contained large areas of hemorrhage, particularly toward the tail. The liver, which weighed 1,250 Gm., the biliary tract, adrenals, kidneys, left tube and ovary, thyroid, and bladder were normal. The ureters were slightly dilated. The right ovary and tube were adherent to the parietal peritoneum in the right lower quadrant of the abdomen. The uterus extended to the level of the umbilicus, and, except for a deep incision 6 cm. in length in the anterior midline of the cervix, showed nothing inconsistent with those of the usual puerperal uterus. There was considerable air under the posterior parietal peritoneum.

The aorta showed slight atherosclerosis. The brain, which weighed 1,140 Gm., and its coverings were not unusual.

A culture of post-mortem blood from the heart remained sterile. The blood urea nitrogen was 14.7 and the creatinine was 1.0 mg. per cent.

Microscopic study of the stomach revealed widespread hemorrhage, particularly in the submucosa in the area of strangulation and around the perforation. There was no inflammatory reaction. The remainder of the gastrointestinal tract was normal except for heavy vascular congestion in the jejunum. The spleen was intensely congested. The pancreas contained large areas of hemorrhage in the parenchyma and some points of early fat necrosis, but no inflammatory reaction. Fatty metamorphosis of the liver and mild chronic pericholangitis were present. The right Fallopian tube revealed mild chronic salpingitis. Sections of the cardiovascular system, thyroid, urinary tract, the remainder of the internal genitalia, and the brain showed no abnormalities.

Anatomic Diagnoses.—*Diaphragmatic Hernia, Left:* Strangulation of herniated stomach and jejunum with extensive hemorrhage into the stomach wall, possible agonal rupture of the stomach with pneumoperitoneum, pneumothorax, and hydrothorax; torsion and congestion of the spleen; hemorrhage into pancreas with pancreatic necrosis; hemoperitoneum; counterclockwise torsion and shift of the heart to the right; pulmonary atelectasis, partial bilateral; retroperitoneal emphysema; fatty metamorphosis and mild chronic cholangitis of liver; chronic salpingitis; Meckel's diverticulum; patent foramen ovale; polythelia.

COMMENT

Between July 1, 1926, and July 1, 1940, among approximately 190,000 registrations for all causes at the University Hospitals, there have been 45 recognized diaphragmatic hernias, 41 in adults and 4 in infants. In 12 cases the diagnosis was either confirmed or made at autopsy. Thirty-six of the adults were above the age of 40 years and 13 were women. The diagnosis was equivocal in 2 of these women, confirmed at operation in 3, by x-ray studies in 7, and by x-ray and autopsy examination in 1 other. In 5 women the cardiac end of the stomach and in 3 cases the fundus formed the hernial mass. In one other case, both the fundus and cardia protruded into the thoracic cavity, while another showed part of the stomach, colon, and small intestine in the left pleural cavity. Every woman except one had had from 1 to 7 spontaneous deliveries. The histories of the deliveries were recorded as uncomplicated as was also the clinical course of the pregnancies; the only exception to this rule is the case here recorded. Five patients had no symptoms directly attributed to the hernia. Nine individuals had suffered from heartburn and occasional nausea, with vomiting for periods of six weeks to twenty years before the diagnosis was made. Two women gave histories of definite pain associated with deglutition.

According to Rigler and Eneboe¹ the most common diaphragmatic herniation is through the esophageal hiatus; in our group reported here, there were 2 women with a paraesophageal hernia. Rigler and Eneboe made roentgenologic gastric examina-

the ileum, appendix, transverse colon, and cecum. The latter was in the apical portion of the chest cavity.

The right side of the diaphragm appeared normal, while the left presented an oval-shaped defect, the long axis of which was transverse. The opening was in the posterolateral portion of the dome and measured 13 cm. in circumference. Posterior to the defect there was an intervening slip of diaphragmatic muscle and fascia, measuring 2.5 cm. in diameter. The opening had sharp edges. There was no connection with the other apertures, which were normal. Only a small portion of the cardia and the lower segment of the stomach and pylorus were below the diaphragm; the major portion of the organ, which was bent sharply on itself, was in the lower left side of the thorax. The duodenum was sharply curved in the epigastrium and the near-by loops of jejunum were greatly distended. The remainder of the intestines were in the thoracic cavity, except for the lower part

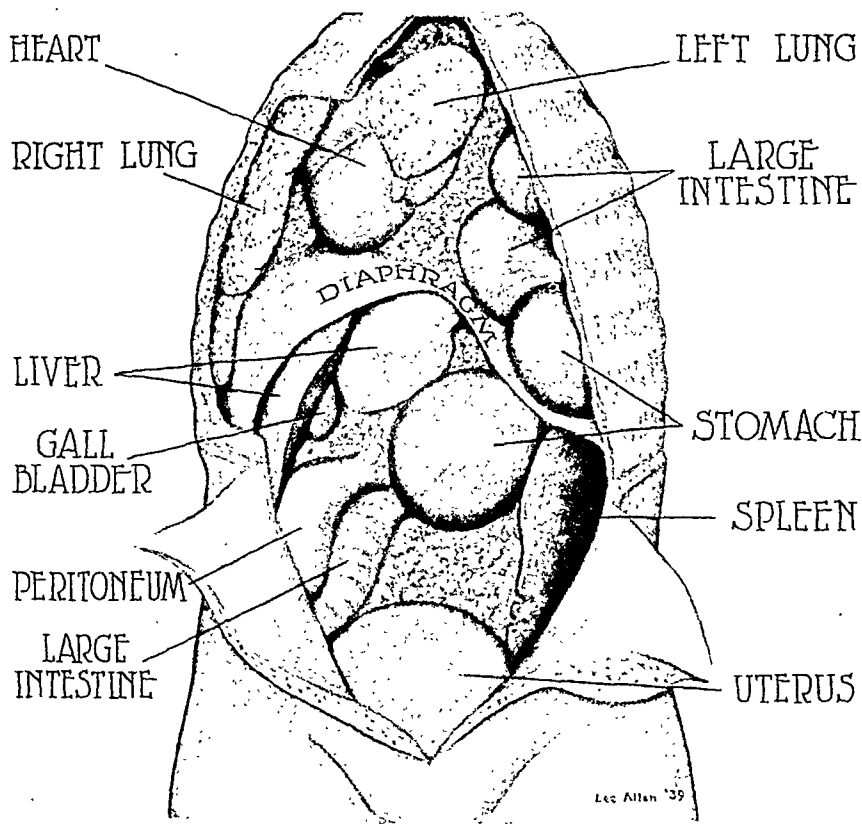


Fig. 1.—Showing the visceral relationships at the time of the autopsy.

of the descending colon which passed back through the defect medial to the posterior cardia and pylorus and lateral to the jejunum. The stomach wall presented a sharply demarcated line of hemorrhagic infiltration at the areas where the cardia and pylorus came in contact with the sharp margin of the diaphragmatic defect. There was a perforation 2 cm. in diameter on the posterior surface of the stomach at the junction of the upper and middle thirds in the region of the edge of the hernia. The intra-abdominal portion of the jejunum showed heavy vascular congestion but no perforation. There was a small amount of bloody fluid in the upper portion of the gastrointestinal tract, and a Meckel's diverticulum, measuring 4 by 2 cm. was present 1.8 meters proximal to the ileocecal valve.

The right pleural cavity contained no excess fluid. The heart and mediastinal structures were pushed far to the right so that the apex of the heart was directly posterior to the fourth costochondral junction on the right. The heart, which had

OVARIAN PREGNANCY, PRIMARY OR SECONDARY?*

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A PRIMARY, or true, ovarian pregnancy, is one in which the ovum, remaining in the follicle, is there fertilized, develops a sac from the contiguous ovarian tissue, and continues its growth in the follicle. In contrast, a secondary ovarian pregnancy is one in which the ovum is fertilized in tissues, tubal or uterine, outside of the ovary, develops its sac from this extraovarian tissue, and after developing its sac, becomes detached from its parent soil and secondarily attaches itself to the ovary. In the case of primary ovarian pregnancy, the sac if not completely ovarian should be so preponderantly. In secondary ovarian pregnancy, the sac is likely to consist of an admixture of both varieties of tissue, ovarian and non-ovarian, but there should be a predominance of tissues from the site of primary fecundation.

The possible mechanism of primary or true ovarian pregnancy is at the present time a matter for speculation. Caturani¹ predicates as its basis a perioophoritis. A second theory postulates the rupture of a centrally placed follicle into a previously vacated surface follicle.² Another theory assumes the retention of Müllerian tissue in the ovary.³ Sutton⁴ formulates a theory based on Sampson's work on endometriosis. To whatever theory we ultimately subscribe, we must accept the existence of two constant factors operating in its etiology, that the ovum remains imprisoned within the cavity of the ruptured follicle, and that the sperm cell finds its way to this particular ovum.

Therefore, one may justly conclude that primary ovarian pregnancy is a rare phenomenon. Many cases reported as primary ovarian pregnancies are excluded by careful reviewers. Thus, Schumann,⁵ in 1921, quoted only 43 cases; Sutton,⁴ in 1924, accepted only 47 cases; Frank,⁶ in 1927, accepted 64, while Wollner,⁷ in 1932, discarded 39 of 87 reported cases. More recently, in 1934, Dodek⁸ referred to only 52 cases of true ovarian pregnancies. Young and Hawk⁹ report one case in a series of 148 cases of ectopic pregnancies, over a period of sixteen years, an incidence of 0.7 per cent. Since then there have been a few reports of additional isolated cases. At our hospital, the case about to be reported is the first noted in a period of over twenty-five years.

CASE REPORT

H. K., married, aged 31 years, was admitted to Gynecologic Service No. 2 of the Mount Sinai Hospital on March 6, 1936, with vaginal bleeding and severe pain in the lower abdomen. Her present illness dates from January 30 of the same year, when after missing a regular period (last regular period Dec. 18, 1935), she was seized suddenly with severe abdominal pain and slight vaginal bleeding. This attack was accompanied by syncope. She was admitted to a neighboring hospital, where a Friedman modification of the Aschheim-Zondek test was positive. A diagnosis of threatened abortion, with a living fetus, was made at that institution. She was given one week of expectant treatment and discharged to the care of her family physician. However, intermittent cramplike pains continued. After four days at home, she returned to the same institution, remaining four additional days under observation, following which she was again discharged. Approximately two weeks later, she was admitted to the Mount Sinai Hospital.

On admission, the patient was found to be well nourished and comparatively comfortable, though complaining of pain and vaginal bleeding. Her temperature was 99.2° F., pulse 100 and of good volume. Tenderness was present over the

*Read at a meeting of the Obstetrical Society of Philadelphia, Pa., May 2, 1940.

tions on 195 women in the third trimester of pregnancy. Small hernias through the esophageal hiatus were found in 18.1 per cent of multiparas and in 12.1 per cent of the entire group. In 7 women of this series presenting definite small hernias, the defect was not demonstrable after parturition. These investigators were unable to correlate the symptoms with the presence of the herniations, but felt that repeated pregnancy in young individuals could lead to the production of these abnormalities.

Four fatal cases²⁻⁴ of diaphragmatic hernia diagnosed during pregnancy have been found in the literature. One woman was operated upon for appendicitis at the sixth lunar month, but the appendix could not be located and the hernia was not found. The patient died a few hours after operation, and at autopsy part of the large and small bowel were found incarcerated through the diaphragmatic defect. The other 3 patients had acute symptoms suggesting ileus at the fourth, eighth, and tenth lunar months, respectively. Two of the 3 hernias were not diagnosed before necropsy, while the third was visualized on roentgenographic films. Two of these women (eight and ten months pregnant) became ill with the onset of labor; one died the day after delivery, while the other lived only a few minutes after the third stage was completed. The third patient died in the fourth month as the result of acute strangulation of the hernia.

From the autopsy and the history it is concluded that the case here recorded represented a congenital hernia. The knowledge that she had previously had 3 normal deliveries and 1 laparotomy without complication argued for conservative management during the fourth pregnancy. Moreover, it seems doubtful whether any form of operative treatment would have been of value after acute symptoms appeared. On the other hand, it would seem justifiable to sterilize an individual who has a hernia of this extent to prevent further pregnancies should the hernia be irreparable, a view which is also held by Granzow.² It has been definitely proved by Mengert and Murphy⁵ that intra-abdominal pressure may increase considerably in the sitting position, and is further accentuated by voluntary muscular effort (Mengert and Murphy⁶) during labor. There is little doubt that the strangulation in this case and in 2 of the others cited was provoked by the increased intra-abdominal pressure associated with the onset of labor.

SUMMARY

Among 13 cases of diaphragmatic hernia found in parous women during the last fourteen years at the University Hospitals, 1 woman died during parturition from strangulation of viscera in a left-sided diaphragmatic hernia. This patient had had 3 previous uncomplicated deliveries.

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bluish and grayish masses resembling placental tissue. No membranes can be seen about the fetus nor can the site of attachment of the umbilical cord to the placental structures be determined at this time. The course of the Fallopian tube on the left side has been sharply distorted, passing downward and anteriorly across the anterior surface of the large mass just described. The tube is moderately thickened but appears intact throughout. Its fimbria are congested."



Fig. 2.—Showing corpus luteum and ovarian stroma. $\times 60$.

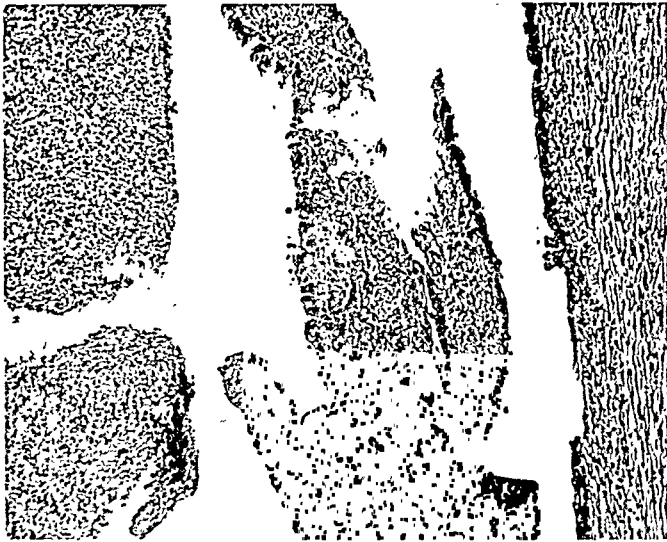


Fig. 3.—Showing portion of wall of sac with epithelial-lined tissue. $\times 80$.

Microscopic.—"The uterine endometrium shows no attached chorionic villi nor any decidual reaction. Both Fallopian tubes show subchronic suppurative processes, involving especially the mucosal layers and the innermost portions of the muscle coats. No decidual reaction is noted in the Fallopian tubes. In the bluish and grayish tissue resembling placenta, observed in the upper portion of the large left-sided ovarian mass already described, are many typical well-preserved chorionic villi, with Langhans and syncytial cell layers (Fig. 1). Other villi are necrotic and hemorrhagic. The corpus luteum described grossly is composed of large lutein cells (Fig. 2). In some of the early sections taken from widely separated

entire lower abdomen, more marked over the left lower quadrant. No rigidity or distention was noted. Bimanual examination revealed a soft cervix with a closed external os. The uterus was enlarged to about the size of a two months' pregnancy, partially movable, with tenderness to the right. A tentative diagnosis of intrauterine pregnancy, complicated by pelvic cellulitis and inevitable abortion was made. The following day, on exploration of the uterus, a small amount of well-preserved decidua was found. Later a mass was palpated closely adherent to and to the right of the uterus. Hemoglobin was 68 per cent (Sahli); red cells, 3,680,000; white cells, 11,900; polymorphonuclear cells, 77 per cent. The urine was essentially negative. Because of the continued pain and increasing size of the pelvic mass, a laparotomy was performed on March 25, 1936. The uterus and adnexa were adherent to the large and small bowels. A tuboovarian abscess was found on the right side. On the left side the tube was adherent to and encircled a large, round, bluish, cystlike structure, occupying the region of the left ovary, measuring approximately 12 cm. in diameter. A supravaginal hysterectomy with a bilateral salpingo-oophorectomy was done. The patient made a complete recovery.

PATHOLOGIC REPORT

Macroscopic.—"The operatively removed specimen consists of a supravaginally amputated uterus and adnexa. The uterus measures 8 by 5 by 4 cm. It is firm in consistency throughout. Its wall is intact at all areas. The endometrial layer is thin and moderately injected.



Fig. 1.—Showing chorionic villi. $\times 60$.

"To the right of the uterus is a tuboovarian abscess. The tube is greatly thickened, measuring 7 by 3 cm. Attached to the left side of the uterus and occupying the site of the left ovary is a large roughly globular, dark plum-colored and grayish mass measuring 11 by 8 by 6 cm. A thin layer of clotted blood is present over a small area of its surface. The surface bulges irregularly, particularly over an area 5.5 by 3.5 cm., the latter bulge being caused by a small thin-walled cyst distinct from the major mass. The major mass, on sectioning, consists of a cystic structure, with a moderately thickened wall. It appears on section to be composed of two portions. The lower smaller portion measures 2 by 6 cm. and consists in part of a large corpus luteum, 19 mm. in length. The remainder of this lower portion is a nondescript tissue, inundated with blood.

"The upper portion is separated from the lower by a thin layer of compressed grayish tissue. This upper portion measures 8 by 6 cm. Lying free within its cavity is a fully formed, well-preserved fetus, 8 cm. in length, to which is attached a narrow umbilical cord. Plastered against the lateral, anterior, and posterior walls of this cavity and occupying about three-fourths of its volume are firm,

been subjected to pressure and to penetration by blood, so that they are necrotic and partially destroyed.

I belong to the school of thought which was inaugurated by Webster of Chicago and feel that pregnancy cannot occur in the absence of Müllerian tissue. However, the discovery of the presence of endometrial cells and groups of uterine glands in the ovarian tissue itself, has cleared up this matter, so that it is wholly possible for a pregnancy to occur in an ovary, provided a little endometriosis is present. In the case now under discussion I should agree with Dr. Mann that he is dealing with an ovarian pregnancy.

THE EFFECT OF DIETHYLSTILBESTROL AND DIETHYLSTILBESTROL DIPROPIONATE ON POSTMENOPAUSAL VAGINITIS AND SYMPTOMS

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IT IS to be noted that many American writers have found the stillbestrol compounds quite effective as estrogenic agents and giving excellent relief for menopausal symptoms. The so-called toxic effects of nausea and vomiting have almost entirely followed the oral preparations. In contrast to the opinion of Schorr, Robinson and Papanicolaou¹ they have been much less frequent and have extremely rarely followed intramuscular injections. According to the *Lancet*² extensive use of stillbestrol in England "does not reveal a high proportion of unpleasant side effects."

MATERIAL

In the present study 111 women have been treated for menopausal symptoms and atrophic vaginitis. Sixty-two were given intramuscular injections of diethylstilbestrol dipropionate (Winthrop). Sixty-eight were given diethylstilbestrol by mouth (in 32 cases, Winthrop's uncoated tablets: in 23, Parke Davis plain capsules; in 8, Lilly's uncoated tablets; and in 33, Lilly's enteric coated tablets).^{*} These women were treated an average of three months each, although 39 were treated more than four months, 5 longer than one year, and 2 continuously for sixteen months.

RESULTS

Of the 108 patients with menopausal symptoms 47 per cent had four-plus improvement, 24 per cent three-plus, 9 per cent two-plus, 2 per cent one-plus and 18 per cent no improvement.† In 14 with no atrophy, 4 showed no improvement in symptoms. These findings indicate much poorer results in the relief of menopausal symptoms than in growth effects on the atrophic vagina. Vascular symptoms were almost invariably relieved. All nervous symptoms at the menopause evidently are not caused by a lack of hormone. From our experience these results do not differ materially from those following the natural estrogens. It does not seem that patients treated with stilbestrol have any different feeling of well-being, as compared with those treated with natural estrogens. No definite tolerance or lack of effect has been noted.

^{*}Because of toxic results reported by some observers, the origin of each material is given. The materials have been generously supplied by the Winthrop Chemical Company, Parke, Davis & Company and Eli Lilly Company.

†Improvement was graded from one to four plus.

portions of the wall of the sac enclosing the fetus and placental tissue, are collections of ovarian stroma, occasionally containing a small follicle cyst. Graafian follicles are scanty in this ovarian stroma. The latter shows a decidua-like reaction. However, in sections taken later from the wall of the sac there is observed, often in contact with necrotic tissue containing chorionic villi, layers of tissue lined by a low columnar cell epithelium, resembling Fallopian tube epithelium or parovarian epithelium. In some areas this epithelium covers small papillary projections (Fig. 3). In the underlying wall no distinct muscle layers are present, but there are strands of tissue resembling muscle cells. This epithelial-lined tissue is infiltrated with inflammatory cells. It should be stressed that this tissue constitutes a portion of the wall enclosing the products of conception and that these latter products are apparently compressing it and its papillary projections (Fig. 3).''

COMMENT

Obviously, the case reported is that of some form of ovarian pregnancy. The uterine cavity is empty, the left tube is intact, the sac containing a fetus occupies the position where the ovary should be, and the sac is attached to the uterus by the utero-ovarian ligament. Since these gross criteria of Spiegelberg were fulfilled and since a preliminary microscopic report stated that ovarian tissue was found in different and widely separated sections taken from the sac wall, a *prima facie* case of true ovarian pregnancy appeared established.

Furthermore, from the microscopic studies the additional criteria of both Williams and Norris appeared satisfied. In its entirety, then, this case met not only all the established criteria of ovarian pregnancy but in addition a fetus was found intact in the sac. According to Hunter as quoted by Thro,¹² an embryo was recovered in only 19 instances out of 43 cases.

Having met all the requirements, we were then placed in the anomalous position of having to dispute or, at least, cast a shadow of doubt on the diagnosis of true ovarian pregnancy, because of the presence microscopically in later sections of the epithelial tissue found in different portions of the sac wall as has already been described in the pathologic report.

If this be a primary ovarian pregnancy, the question arises, Why was this epithelial tissue found scattered in different portions of the sac wall? The possibilities are fourfold: contact with the Fallopian tube, contact with an accessory tube, contact with some parovarian tissue, and an endometriosis of the ovary.

We are inclined to consider the possibilities to rest between contact with an accessory tube or contact with some parovarian tissue.

Here then we have a case meeting all the approved criteria of an ovarian pregnancy, and yet there are sufficient anomalous findings which make impossible its unequivocal acceptance as such. The interesting speculation arises, How conclusive are the great majority of cases of so-called primary ovarian pregnancy? Would, as in our case, a more thorough investigation by means of many microscopic sections, have also revealed disturbing findings in many of these reported cases?

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2019 PINE STREET

DISCUSSION

DR. EDWARD A. SCHUMANN.—It is extremely difficult to satisfy all the criteria concerning ovarian pregnancy because so often the walls of the sac have

vented by such a simple method as enteric coating, the seriousness of the reactions could not be great and the main objection would be overcome. No doubt this potent drug, as any other, may be harmful if given excessively. At the present time there seems to be no serious harm in its therapeutic use and certain advantages in its oral use and low cost.

SUMMARY

1. One hundred and eleven patients with menopausal symptoms and atrophic vaginitis have been treated with diethylstilbestrol and diethylstilbestrol dipropionate for an average of three months each.

2. The results seem entirely comparable with the natural estrogenic hormones.

3. Nausea and vomiting from oral preparations apparently may be relieved if the material is enteric coated.

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DERMOID CYSTS OF THE OVARY

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THIS is a study of dermoid cysts of the ovary removed at operation at the Cook County Hospital. In the files of the surgical pathology laboratory covering a period of ten and one-half years, from July, 1928, to December, 1938, a total of 121 cases of dermoid cysts of the ovary is listed. These dermoid cysts comprise 14.9 per cent of all benign and malignant ovarian tumor studies, excluding enlargements of the ovary due to simple follicular cysts and corpora hemorrhagica. Unfortunately only 103 of the histories of the above 121 cases were obtainable. The remainder of the paper is a study of these 103 cases.

Simple dermoid cysts or benign cystic teratomas have been well known for many years and were thoroughly reviewed by Miller¹ in 1937. However, Miller collected only 953 cases in which the site of the tumor was given. (Complete references to this subject can be found in Miller's paper.)

The average age incidence in this series (Fig. 1) is 32.8 years, which is similar to the figure given by Kouchy² in this country as 38.37. There were 78.4 per cent of the cases which occurred between the ages of 20 and 45 years, with a peak between 35 and 39 years. Marital histories were obtained in 88 cases, of which 31 denied pregnancy and 57 had been pregnant a total of 159 times. From these pregnancies there had been a total of 115 live births. Of the 57 cases there had been an average gravidity of 2.8 and an average parity of 2.0.

The race of the patients is stated in 76 cases, of which 55.3 per cent were colored and the rest white.

The location of the tumor was known in 87 cases, of which in this series, 58.6 per cent were in the right ovary, 33.3 per cent in the left ovary, and 8.1 per cent were bilateral. In the 953 cases collected by Miller, 45.0 per cent were in the right ovary, 39.2 per cent in the left ovary, and 15.2 per cent bilateral.

Of the 97 patients with atrophic changes in the vagina, 73 per cent showed four-plus improvement, 20 per cent three-plus, 4 per cent two-plus, and 3 per cent no effect. Probably the complete growth effect can be obtained in any case if sufficient material is given. In the 3 per cent without evident effect very slight atrophic changes were present and relatively small doses were given.

DOSAGE

The dosage of these materials has varied most widely. From 0.05 mg. to 5 mg. have been given parenterally, repeated daily or as infrequently as two weeks. By mouth from 1 to 5 mg. have been given daily or at longer intervals. From these studies most satisfactory results have followed these methods: parenterally, 1 mg. each week for two or three weeks, followed by 1 mg. every two to four weeks as long as necessary; orally, 1 mg. daily for six to twelve days, followed by 1 mg. two or three times weekly as long as necessary. Many of the complications described below have followed much larger doses.

COMPLICATIONS

One patient developed a basal cell epithelioma of the nose while receiving 21 mg. by injection over two and one-half months. Any definite causal connection is uncertain.

Postmenopausal bleeding occurred in 12 cases, lasting from one to fourteen days, at times profuse. Later in the study it was evident that often the dosages were too high, although one patient bled several times after very small amounts.

Breast symptoms developed in four patients, three complaining of fullness and one of soreness. No tumors were noted.

A rash over the abdomen appeared in one case early in treatment. After the rash disappeared treatment was resumed. During six and one-half months of further treatment no eruption reappeared.

One patient complained of nightmares while taking oral medication. The nightmares stopped when the medication was discontinued, only to reappear when the oral stilbestrol was resumed. Later injections of the dipropionate were accompanied by no nightmares and relief of nervous symptoms.

Nausea and vomiting occurred in two patients after parenteral injections. In each case the symptoms followed 5 mg. injections and were not present during subsequent treatment with smaller dosages.

Nausea and vomiting followed oral medication in 17 cases (25 per cent of those receiving oral material). In 10 of these there was only nausea and no vomiting. In 5 the nausea wore off as the drug was continued, and in a sixth nausea appeared only after twenty days with 1 mg. daily. In 7 cases there was also vomiting. An analysis of the different commercial products shows these symptoms occurred as follows: 10 in 32 with Winthrop's plain tablets, 7 in 23 with Parke Davis plain capsules, 1 in 8 with Lilly's plain tablets, and 1 in 33 with Lilly's enteric coated tablets.

The enteric coated oral material is of particular interest. In 33 cases, only one had nausea and vomiting. This patient had had frequent nausea and vomiting before taking the medication, which continued after the drug was stopped. No other patient offered any digestive complaint. In 3 of the above patients with nausea and vomiting from the uncoated material, such symptoms disappeared when the enteric coated drug was given.

The fact that enteric coating apparently prevents nausea and vomiting from the oral preparations may lead to a different consideration of this drug. At the present time the great fear of toxic reactions has prevented its general use. Certainly the most common toxic reaction has been of gastrointestinal origin. If these symptoms can be pre-

X-ray has often been used for the visualization of teeth or bone in these tumors, but was not used in any of these cases.

TABLE II. PREOPERATIVE DIAGNOSES

	NUMBER OF CASES		PERCENTAGE OF CASES
Ovary			
Dermoids	3	3	3.1
Other tumors, usually cysts	30	30	30.9
Uterus, fibroids	38	38	39.2
Fallopian tubes			
Chronic salpingitis and chronic abscesses	13	16	16.5
Ectopic pregnancy	3		
Appendicitis	4	4	4.1
Other conditions			
Tumor, location not stated	1	6	6.2
Pelvic peritonitis	1		
Hematometria	1		
Prolapse of the uterus	2		
Pregnancy	1		
Total	97		100

TABLE III. CAUSE OF SYMPTOMS

	NUMBER OF CASES		PERCENTAGE OF CASES
Ovary			
Dermoid mass	29	37	38.1
strangulation	8		
Other tumors	10	10	10.3
Fallopian tubes			
Chronic salpingitis or hydrosalpinx	15	15	15.5
Uterus			
Fibroids	20	20	20.6
Other conditions as acute appendicitis and prolapse of the uterus, etc.	7	7	7.2
Symptoms not due to any one cause	8	8	8.3
Total	97		100.0

The cause of the symptoms (Table III) as far as could be determined was the dermoid mass in 29 out of a total of 97 instances, and the symptoms were caused by strangulation of the mass in 8 others, making a total of 37 cases, or 38.1 per cent, in which symptoms could be directly traced to the dermoid cyst. Coincident salpingitis or hydrosalpinx was the cause of symptoms in 15 cases; other tumors of the ovary, usually simple serous cysts in 10, and fibroids of the uterus caused the symptoms in 20 instances. In 7 other cases dermoids were found incidentally to such other conditions as acute appendicitis and prolapse of the uterus, while in the remaining 8 cases, the symptoms did not seem definitely related to any one cause.

In conclusion, although dermoid cysts are one of the commonest ovarian tumors, they are seldom diagnosed preoperatively, because of the indefinite symptoms they produce. Very often they are incident to other pelvic conditions.

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Absolutely no correlation could be found between the size of the tumor, the age of the patient, the duration of symptoms, or the number of times the patient had been pregnant.

The presenting symptoms (Table I) were chiefly of pain, usually in the abdomen, or of swelling of the abdomen. These were found in 49.4 and 29.2 per cent, respectively. The next most frequent complaint was menstrual changes, and was given in 15.7 per cent of the cases.

TABLE I. CHIEF COMPLAINT ON ADMISSION

	NUMBER OF CASES		PERCENTAGE OF CASES
Pain in the abdomen	41	44	49.4
in the back	3		
Swelling or tumor of abdomen	26	26	29.2
Menstrual changes			
Menorrhagia or bleeding	6	14	15.7
Dysmenorrhea	2		
Amenorrhea	4		
Irregular menses	2		
Other complaints			
Vaginal discharge	1	5	5.6
Pregnancy	2		
Prolapse of the uterus	1		
Urinary symptoms	1		
Total	89		99.9

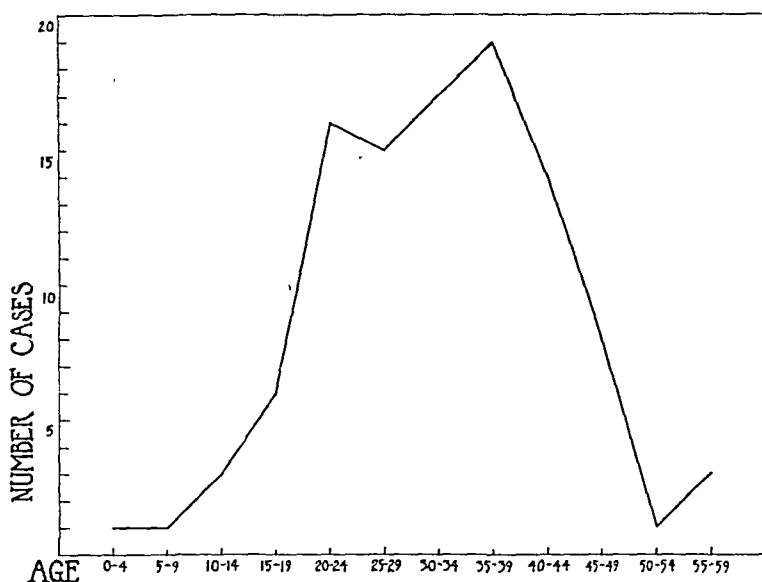


Fig. 1.

The dermoid cysts were correctly diagnosed preoperatively (Table II) in only 3.1 per cent of the cases, but the diagnosis of ovarian tumor or cyst was made in 30.9 per cent of the cases. The other common preoperative diagnoses were uterine fibroids in 39.2 per cent, and chronic salpingitis or tuboovarian abscess in 13.4 per cent. Of the three cases diagnosed preoperatively, one was in a five-year-old girl with an abdominal mass 9 cm. in diameter present for one month and a history of abdominal cramps for one year. The second was made in a 29-year-old woman with a similar sized mass present for four years. The third was in a 21-year-old woman who had had a large abdominal mass for two years. In all of these cases the tumor was large, and in the two adults had been present for two and four years.

The average age of all patients sterilized was 27.83; the average parity at time of operation was 5.04. The number of dead babies was 0.68 each, spontaneous abortions 1.0, and induced abortions 0.3. Nine patients had had previous lower abdominal operations, and one had had drainage of the cul-de-sac. Thirteen patients had a hemoglobin of 50 per cent or less at the time of operation. Seventeen patients were medically induced.

Only two patients who would have been sterilized were refused operation due to their condition. Both were grossly infected on admission to the hospital and ran a long febrile post-partum course. Two others were postponed three days because of fear of infection.

Preoperative medication was given routinely to the patients. Three grains of nembutal were given one hour before operation and $\frac{1}{4}$ gr. of morphine with $\frac{1}{150}$ gr. of scopolamine three-fourths of an hour before operation. The amounts varied somewhat depending on the size of the patient. Almost none of the patients had any memory of leaving their room, and they usually slept through the entire operative procedure. Postoperatively only codeine and aspirin were given, and we have not noticed that these were given with much greater frequency than to other post-partum patients.

Routinely, operations were done with local infiltration anesthesia of 0.5 per cent novocaine. A short paramedian incision was made just below the level of the umbilicus and the tubes brought into the field by hooking a finger over the round ligaments and rolling the uterus from side to side. In each case the tube was grasped in its midportion with an Allis forceps and clamped across the loop gently with a large Kelly forceps about 1 cm. from the Allis. A single tie of black silk was placed about the loop and usually an additional tie was placed through the mesosalpinx and around the tube in the tied-off loop of the tube. We endeavored to tie the first tie snugly but not so tightly as to cut the peritoneum. Closure of the abdomen was made with silk. Twenty or more minutes were usually required to complete the procedure.

Often we found a greater or less degree of edema of the Fallopian tubes, so that they resembled the round ligaments. Twice interns had attempted to tie the round ligament before attention was called to their error. On three occasions we have noticed thrombosed veins in the broad ligaments, but only once did these give later trouble. The gut is frequently not seen and only rarely does the patient cause trouble by pushing out a loop of gut. There is a minimal disturbance of tissue and no intra-abdominal bleeding.

For economic reasons and convenience to the patient, other relatively minor operations may be easily done while the patient is under the influence of deep sedation. One umbilical and two inguinal hernias have been repaired at the same time, and all patients were afebrile postoperatively. On one occasion where symptoms of acute appendicitis were presented, an appendectomy was done at the time of sterilization, in which case the patient was febrile the first four postoperative days. However, appendectomies would eventually lead to trouble and should certainly be discouraged at this time. Almost never do we do any exploration, however slight.

Using the morbidity standard advocated by the American Committee on Maternal Welfare, the incidence of febrile morbidity of all patients was 18.3 per cent. Table II shows rather definitely that the lowest morbidity is found in patients operated

TABLE II. SUMMARY OF MORBIDITY COMPARISON

HOURS POST PARTUM	PATIENTS OPERATED	PATIENTS FEBRILE	PER CENT FEBRILE
0-6	29	4	13.8
6-12	44	6	13.6
12-18	36	6	16.6
18-24	18	4	22.6
24-30	19	4	21.0
30-72	19	6	31.5

upon in the first few hours after delivery. The incidence in 73 patients operated upon within the first twelve hours after delivery was 13.7 per cent. This compares

POST-PARTUM STERILIZATION

R. E. PFUETZE, M.D., SAN JUAN, PUERTO RICO

(From the Presbyterian Hospital)

DURING the past twenty-eight months, 165 post-partum patients have been sterilized at the Presbyterian Hospital at San Juan. This is the largest series yet reported. Recently Adair and Brown reported 50 and Hewitt and Whitley 100 cases; both groups were selected to insure freedom from infection and ease of operation. Our series has been relatively unselected and done at varying intervals of time post-partum.

It is rarely convenient for us to operate immediately following delivery. For this reason the delay in almost every case was due to the convenience of time rather than the condition of the patient. Of the 165 patients, 127 were operated upon in the first twenty-four hours, 33 in the second twenty-four hours, 3 on the third day, one on the fourth day, and one on the fifth day, an eclamptic patient unconscious for four days and markedly toxic. The average length of time was 17.5 hours.

Patients for whom sterilization was recommended were almost entirely ward patients. Private patients usually have access to and are more able or willing to use other less permanent forms of contraception. As soon as it became known that we were doing this type of sterilization, we were deluged with requests, and if for no other reason than self-defense, we have been very strict in the indications. These have been as varied as any given in previous papers, as is indicated in Table I. The greater the parity the less we require of good medical

TABLE I. PRIMARY INDICATIONS

Heart disease	4	Contraception for future operations	9
Toxemias of pregnancy and hypertension	6	Markedly contracted pelvis	8
Syphilis	4	Epilepsy	3
Previous section	1	Schistosomiasis	1
Multiple pregnancies	63	Chronic tropical lymphangitis	3
Pulmonary tuberculosis	5	Social and economic indications	56
Recurrent pyelitis	2		

indications. However, patients for whom sterilization was recommended due to multiple pregnancies or economic and social considerations had also as a major concurrent consideration the danger of additional pregnancies to their health and life. Due to the local conditions of gross over-population, increasing at the rate of 30,000 a year, or 9 per square mile per year, and the inability of the island to produce the bare necessities of life, the fear of endangering the future population was reduced to a minimum.

AN "AUTOMATIC" POST-PARTUM UTERINE PACKER*

RICHARD TORPIN, M.D., AUGUSTA, GA.

(From the Department of Obstetrics and Gynecology, University of Georgia School of Medicine)

IN FEW other surgical procedures is time quite so much a vital factor as in the operation of uterine packing for post-partum hemorrhage. In the excitement of sudden and severe bleeding, the sterility of the procedure is often neglected and the pack is dragged over unsterile portions of the body. Furthermore with the usually available instruments, the introduction of the pack into the top of the fundal cavity is difficult and often unsuccessful, and the uterus bleeds above the gauze, nullifying the beneficial aspects of an otherwise most effective and life-saving procedure. Of course, the administration of pituitrin preparations and of ergonovine intravenously if necessary, after the birth of the portion of the greatest diameter of the child, should be more or less routine.

To facilitate the obstetric operation of uterine packing for post-partum hemorrhage so that within one or two minutes the pack may be introduced aseptically into the very apex and horns of the uterine cavity, the herein described instrument is offered. It is a large size modified Holmes packer with, as an integral part, a container for the requisite gauze pack. The length of the tube is about 6 inches and its diameter $\frac{3}{4}$ inches. The large hole is for loading the pack and the small ones (advised by a former resident, Dr. W. W. Coppedge) are for introduction of an antiseptic as hexylresorcinol S.T. 37 to reduce bacterial growth after the pack is in place.

The Method of Use.—The device loaded, wrapped in towels, and sterilized in the autoclave is kept sterile. When puerperal uterine bleeding is severe, the obstetrician introduces his sterile-gloved left hand high into the uterine cavity. It is of advantage to have someone to hold the fundus through the abdominal wall. The nurse unwraps and presents the packer. The obstetrician introduces his right index and middle fingers into the finger holds and his thumb into the ring of the obturator piston. The introducing tube is then gently pushed through the vagina and cervix into the hollow of his left hand in the uterine cavity. The pack is then displaced by the obturator into the uterine cavity. At the same time if the body of the packer is moved from side-to-side, the pack is snugly and entirely aseptically inserted across the top of the uterine cavity. All of the pack is expelled gradually, elevating and filling the uterine cavity and upper portion of the vagina. It may be removed in twenty-four to thirty-six hours.

While the name "automatic uterine packer" is a misnomer it is of advantage in that it affords an accurate mental picture to the nurse and obstetrician for its use on short notice.

Notwithstanding routine use of pituitrin and ergonovine, it has been found from a study of the records that about one in 200 women in labor bleed following delivery enough to be classed as post-partum hemorrhage.

The following are case reports of 11 such patients. Post-partum hemorrhage from this study is more common in white than in negro women.

CASE 1.—White woman, aged 24 years, para iii, well-nourished with mild toxemia of pregnancy, delivered her third child, $7\frac{1}{2}$ pounds, at home. She bled too much (the students estimated 2 liters), and continued to ooze and was sent to the hospital where upon pressing upon the fundus a blood clot the size of a fetal head was expelled. The uterus failed to remain firm. She became nauseated and vomited, and her skin became clammy, and the pulse rapid. She was taken to the delivery room and prepared for operation. No tear was found in the perineum or cervix. The

*Manufactured by the Sklar Instrument Co., Long Island City, N. Y.

favorably with all of our post-partum patients during this same period, of whom 18.6 per cent were morbid. However, if we compare it with only the multiparas not sterilized during this period, the comparison is not so favorable, as these patients had only a 9 per cent morbidity. We are unable to account for this, considering the lack of symptoms relative to the operation, but can attribute some of it to urinary tract infections abetted by the dehydration of the patient on the day of the operation. Only three patients remained in the hospital more than twelve days. One of these had phlebitis of the leg and was discharged on the thirty-fourth day. Another had phlebitis of the veins of the broad ligaments and was discharged on the twenty-seventh day. In this case thrombosis of the veins of one side of the broad ligaments was observed at the time of operation and pain developed on this side first. These are the only two patients having thrombosis or phlebitis in this series. They were operated upon twelve and twenty-two hours after delivery, respectively. The third patient remained in the hospital fifteen days because of an attack of cholecystitis and cholelithiasis. None of the patients were at any time critically ill and in none could the infection be definitely attributed to the operation itself, although in the case of the patient having pelvic phlebitis, the sterilization was undoubtedly a large contributory factor. Of 11 patients who had vaginal examinations or manipulations, 5 were febrile; however, the indication for manipulation may have contributed also. The average postoperative stay before discharge was 9.4 days. Of 4 patients complaining of some degree of pelvic tenderness several weeks following delivery, 3 had been febrile in the hospital. There were no wound infections and there were no deaths.

Of the 165 patients sterilized, we know of 3 who have become pregnant again at intervals of three, four, and five months following operation. We reoperated upon two of the patients after the second delivery, removing the proximal portions of the Fallopian tube for examination and found that in one case a fistula had developed to the lumen of the proximal portion and in the other the atrophy of the tied-off portion was incomplete. Madlener suggested that the tie be made toward the outer portion of the tube, and findings in the two above cases would indicate this, as in both the tubes were tied quite close to the uterus. While in other patients on whom we have reoperated for other reasons and who have not become pregnant, the tie was found in the middle or outer portion with a section approximately 1 cm. long in which the tube was completely atrophied. No adhesions have been found either to the parietal or visceral peritoneum in any of these re-operated cases.

CONCLUSIONS

The operation in general is a safe procedure, and easily accomplished with no unusual discomfort to the patient nor danger to her life. As has been pointed out by previous writers and as is borne out by these statistics, the sooner the operation is done following delivery the lower will be the incidence of fever. In addition, the operation is more easily done when the uterus is large and the intestines are held away from the incision by its mass.

The greatest deterrent to pointing out the ease and safety of this operation is, that it may be too facilely performed on the post-partum mother who says, "no more babies," resulting in future sorrow and regret by the patient and an increased shortage of children in future generations.

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Adair and Brown: AM. J. OBST. & GYNEC. 37: 472, 1939. *Hewitt and Whitley:* Ibid. 39: 649, 1940.

pelvic inlet AP 12 cm., transverse 14 cm., and good outlet, but the posterior hand prolapsed alongside of the cheek. She was delivered by low forceps from an L.O.A. presentation. The child, weighing 7 pounds 3 ounces, was resuscitated with difficulty but lived. The placenta was promptly expelled, but there was considerable bleeding vaginally in spite of pituitrin, ergot, and uterine massage. A pack was inserted with the use of the automatic packer, and she recovered without further bleeding. She had no fever at any time throughout her stay of one week.

CASE 6.—White woman, aged 22 years, well nourished, para ii, was sent into the hospital because of prolonged first stage of labor, twenty-six hours and forty-five minutes. The second stage was very short, and she spontaneously delivered an 8 pound 4½ ounce normal female child.

Immediately following, in spite of several ampoules of pituitrin and ergot preparations, she had severe vaginal bleeding and developed a state of surgical shock with a blood pressure 60/40 and cold and clammy skin. Her uterus was packed with the automatic packer, and she was given two transfusions of 500 c.c. and 300 c.c., respectively. She recovered rapidly and went home on the seventh day. Her highest temperature was 100° F. once each on two days.

CASE 7.—White woman, aged 31 years, para ii, well nourished, had a short first stage and a rather long second stage, over two hours. The large head was then found to be in R.O.P. It was normally rotated to R.O.T. and Kjelland application of Kjelland forceps made, and with two pulls of forty-five seconds each at intervals of one and one-half minutes, the 7 pound 11 ounce baby was easily delivered. There was a first degree tear of the perineum, which was repaired. She then bled profusely from the fundus which was firmly packed with the use of the automatic packer. While the pack was in place, her temperature was 100° F. When it was removed at twenty-four hours, the temperature remained normal, and she went home on the third day. The attending physician stated that near the end of the first stage of labor the patient had been given 3 mm. of pituitrin subcutaneously.

CASE 8.—White woman, aged 27 years, para iii, delivered a 9-pound baby on the outpatient service and was sent into the hospital because of retained placenta. At the end of five hours this was removed manually from the upper posterior wall, following which there was a tendency for the fundus to bleed. There was no evidence of injury. Her blood pressure dropped to 80/60, and the uterus was packed with the use of the automatic packer. Following this, she was given three blood transfusions, totalling 1,000 c.c. The pack was removed at thirty-six hours, and there is no record of any subsequent bleeding. While the pack was in place, the temperature was normal. After its removal, fever of 101° F. was observed once on each of two days. When she was dismissed on the tenth day, she had 3,520,000 red blood count per c.mm.

CASE 9.—Negro woman, aged 20 years, of medium constitutional type, after normal labor, delivered a 7-pound 5-ounce baby by breech presentation. Notwithstanding the administration of pituitrin and ergot preparation, she bled profusely from the uterus. There was found slight injury to the cervix and perineum. Her uterus was packed with the use of the automatic packer. At the time of inserting the pack, her temperature was 102° F.; pulse rate, 128. The pack was removed at the end of thirty-six hours, and there was no bleeding. She recovered rapidly and went home on the sixth day.

CASE 10.—White woman, aged 22 years, medium constitutional type, had a normal delivery of a 7-pound 12½-ounce baby. Following normal delivery of the placenta, there was profuse vaginal bleeding. There was some laceration of the cervix which was repaired by catgut sutures. The fundus was packed, using the automatic packer, and the pack controlled the hemorrhage completely. It was removed at the end of twenty-four hours, and the patient fully recovered without fever and went home on the third day.

CASE 11.—White woman, aged 20 years, in her second pregnancy went into premature labor with a transverse presentation and a prolapse of a fetal arm. She was

uterine cavity was packed with sterile gauze with the use of the automatic packer. The pack was removed in twenty-four hours and no bleeding ensued.

Her temperature on admission was 102° F. After the insertion of the pack she was given a transfusion of 500 c.c. of citrated blood. Her temperature the second day went to 103° F., not quite so high the third day, and thereafter fell rapidly to normal. She was dismissed as recovered on the seventh day.

CASE 2.—White woman, aged 34 years, well-nourished para v, had had a fairly normal pregnancy, but she went into labor with transverse presentation breech left, head right, with left arm prolapsed through dilating cervix. She was ordered treated by large Voorhees' bag insertion to be followed by podalic version and extraction. However, the cervix was found to be fully dilated, consequently the child was then turned and delivered. No lacerations of the fundus, cervix, or perineum were found. In spite of pituitrin and ergot and constant massage of the uterus, she continued to bleed for two hours, when she was returned to the delivery room and a fundal pack was inserted by use of the automatic packer. The pack stopped the bleeding entirely, and was removed in thirty-six hours. At no time did her temperature rise above 98.6° F. Inasmuch as her hemoglobin remained high, 12 Gm. per 100 c.c., she was not given a transfusion.

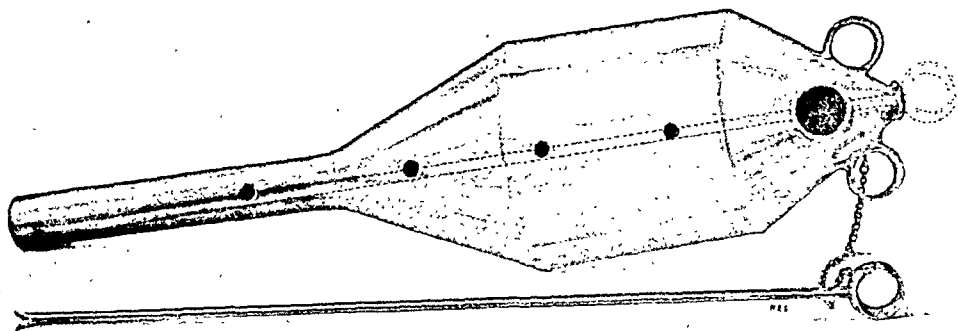


Fig. 1.

CASE 3.—Negro woman, aged 17 years, para ii, while in the emergency room delivered a 7-pound, 12-ounce baby without apparent injury to her cervix or perineum. She continued to bleed vaginally in spite of repeated administration of pituitrin and ergot preparations and massage of the uterus. The following note four hours post partum is self-explanatory: "Blood pressure 98/60; continues to ooze from vagina—has had ergotrate intravenously, etc. So under sterile precautions cervix visualized, seemed OK, but continuous oozing was seen coming from os. Packed with automatic uterine packer intrauterine and intravaginally. Blood pressure 65/20." She bled no more and her blood pressure returned to normal. The pack was removed in thirty-six hours. Her temperature, while the pack was in place, rose to 100.4° F. once and 102° F. on the third day. After this, the temperature rapidly returned to normal. Her hemoglobin was recorded as 6.5 Gm. and her red cells as 2,440,000. She should have had a transfusion but went home otherwise recovered on the twelfth day.

CASE 4.—White woman, aged 24 years, slight obese constitutional type, with mild toxemia, was sent into the hospital from home delivery service two hours after completion of a long labor since when there had been constant bleeding vaginally. She was in mild surgical shock. She was prepared for operation, and her uterus was found to be full of clots which were removed and the fundus packed with use of the automatic packer. She was then given 500 c.c. of citrated blood. The pack was removed in thirty-six hours, and no bleeding followed.

She developed no fever and went home on the fifth day with not quite 4,000,000 red cells per c.mm. and 65 per cent hemoglobin.

CASE 5.—White woman, aged 22 years, obese type, primipara, was in labor a total of twenty-six hours and thirty minutes with a long second stage. She had a large

Vaginal examination revealed the cervix completely dilated. Fetal hearts were still present, approximately 170. No progress for the past two hours.

Under ether anesthesia a breech extraction was attempted with no success except a descent of the first child to the level of the sacrum. The presence of fetal intestines was noted in the vaginal canal and on examination the presence of Siamese twins was recognized and operative delivery was instituted.

Episiotomy, deep mediolateral, and destructive operation performed on the first twin by severing the anterior and posterior arms at the shoulder. Craniotomy performed through the roof of the mouth followed by severance of the thoracic attachment and delivery of the first twin. The arms were severed first. The second child was extracted with no difficulty. Both were stillborn, weighing 3 pounds 13 ounces and measuring 17.5 inches in length, and 4 pounds 3 ounces and 17 inches in length, respectively. Both were females.

During the above operative delivery the patient developed severe shock, which was controlled with 2,000 c.c. of glucose and later with 500 c.c. of blood.

Immediately following the birth of the twins the placenta was delivered manually and during this procedure the presence of the third fetus was ascertained and delivered by version and extraction. This was a living female child, weighing 4 pounds 15 ounces, followed by manual extraction of the second placenta. The third fetus was perfectly normal and was resuscitated with little difficulty, despite the fact of the long operative delivery and prolonged anesthesia.

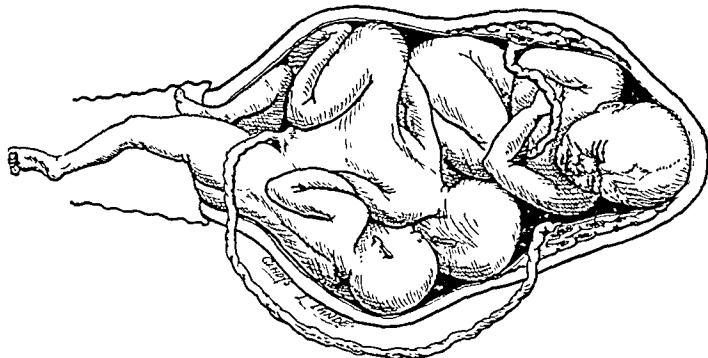


Fig. 1.

Immediate postpartum condition was poor. No effort was made to repair the cervix or perineum. The uterus and vagina were packed and the patient given ergotrate intravenously and ergometrine intramuscularly to control the excessive hemorrhage, and she was sent back to bed.

Patient received a second 500 c.c. blood transfusion on her first day of the puerperium and a third on her ninth day. The pack was removed in twenty-four hours. Ten grains of sulfanilamide were given, four doses daily, for four days. The in-lying catheter which was introduced in the delivery room at the termination of the delivery was allowed to remain in the bladder for three days, due to the marked edema of the vulva and vaginal walls. One gallon hot saline douches were given daily.

Her puerperium was uneventful, highest temperature 101.4° F. Fever disappeared by gradual lysis and she was discharged from the hospital on her twenty-second postpartum day. Pelvis was negative on discharge, except for a granulating episiotomy and perineal laceration.

This patient subsequently received treatment in our out-patient gynecologic clinic and was readmitted to the hospital in April, 1940, for perineorrhaphy. The cervix having healed spontaneously, no operative therapy was deemed necessary.

Mother and child were in excellent condition on last visit to the out-patient department for postoperative check-up.

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- (1) *Ilberg, George*: Ztschr. f. Geburtsh. u. Gynäk. 117: 492, 1938; 119: 369, 1939.

anesthetized and delivered by version and rather difficult extraction. The baby, which was stillborn, weighed 4 pounds 12½ ounces. Following delivery, the uterus bled profusely in spite of pituitary and ergot extracts and was packed from the automatic uterine packer. This completely controlled the bleeding and the pack was removed at the end of twenty-four hours, following which the patient had no elevation of temperature above normal. She went home on the third day.

CONCLUSIONS

1. All of these cases were failures in regard to control of uterine hemorrhage by oxytocic pituitrin and ergot preparations, even intravenously administered.
2. In each the bleeding was completely and immediately controlled by this method of packing.
3. In none was there evidence of any infection produced.
4. An easily comprehensible, compact, and efficient device is described for the performance of this frequently neglected life-saving operation.

SIAMESE TWINS (THORACOPAGIC) COMPLICATING TRIPLET PREGNANCY*

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THIS congenital abnormality is so rare that a careful review of the recent literature shows only one similar case report. Ilberg¹ reports a case seen at the State Woman's Clinic at Dresden, in March, 1939.

This was a 41-year-old, para ii, delivered by a midwife of stillborn Siamese twins, followed by a third fetus which lived for twelve hours. All were at term, all females and having one placenta for the twins and one for the single fetus.

We are, therefore, reporting our experience because of the rarity of such cases and in view of the fact that we delivered one living child, after a very difficult labor.

Mrs. H. T., an Italian housewife, aged 25 years, registered in our prenatal clinic in July, 1939. On admission she was approximately four months pregnant, with no complaints. Last menses occurred March 19, 1939. Calculated date of confinement was Dec. 26, 1939.

Family history and past personal history were essentially negative. Physical examination revealed no pathology.

The height of the fundus was 20 cm. Pelvimetry was normal.

Her prenatal course was uneventful and she was admitted to the hospital in labor on Nov. 27, 1939, at 11 A.M., one month before the calculated date of confinement.

Pains began at 9:30 A.M. on November 27, and the membranes ruptured at home.

On admission, physical examination was normal except a blood pressure of 152/100. Urinalysis showed a heavy trace of albumin.

Abdominal examination revealed the presence of twins, R.S.A. and L.S.P. Two fetal hearts were auscultated, one on the right side near the umbilicus and the other laterally on the left side. Rectal examination revealed a breech presentation with no cervical dilatation.

The patient was considered a normal case for spontaneous delivery (blood pressure subsequently dropped to 130/90) and was allowed to progress in this manner. At 10 P.M. after approximately eleven hours in labor she was transferred to the delivery room with a footling presentation.

*Presented at a meeting of the Obstetrical Society of Philadelphia, October 3, 1940.

and lymph nodes all failed to show on gross or microscopic examination any evidence of metastases. There were no pathologic changes in the heart suggestive of organic heart disease. The tumor was described microscopically as being formed of large and small areas of atypical smooth muscle cells which varied in size and shape. The nuclei were spindle, round, or polygonal in shape, hyperchromatic and revealed numerous atypical mitoses. Between the muscle bundles were many large and small areas of typical myxomatous change containing occasional stellate cells. Several smaller tumor masses of the uterus revealed on microscopic examination the typical changes of benign uterine myomas.

The pathologic diagnosis was: multiple myomas and multiple leiomyomyxosarcomas of the uterus with peritoneal sarcomatosis.

I wish to express my thanks to Drs. J. G. Sharnoff and Cyril Solomon from whose autopsy and pathologic reports the latter part of this paper freely quotes.

AN IMPROVED INSUFFLATION CANNULA

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TUBAL insufflation and uterosalpingography recently was made easier and more accurate through the designing, by E. D. Colvin,¹ of a screw tip cannula, which, without pain, may be screwed into the external os of the cervix tightly enough to ensure against leakage, without need for tenaculum or traction on the cervix. We have incorporated into this cannula (*A*) a stylet cannula (*B*), similar to that of an old style insufflator, except that the end is closed and the openings are on the side (*C*), thus allowing a smaller tip, which will pass through the internal os easier and at the same time lessen danger of traumatizing tissue with the sharp open end. We feel that the stylet cannula reaching into the fundus acts as a guide for the screw cannula, obviating any false passage, and also insures that a tight internal os does not cause obstruction. In addition, it prevents obstruction due to acute angulation of the cervix on the body.

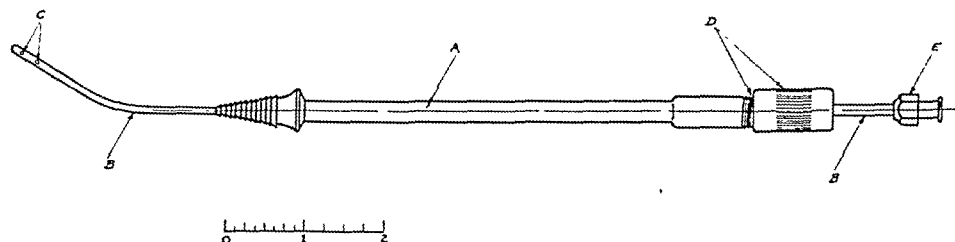


Fig. 1.

At the proximal end of the screw cannula is a lock joint (*D*) which works by screwing down, thus compressing a small section of rubber tubing as an expanding washer, and forming an airtight seal. At the proximal end of the instrument, which is, of course, the end of the inner cannula, a Luer Lok connection (*E*) is screwed on so that a syringe may be applied directly for salpingogram injections, or for a Luer Lok connection with an insufflation apparatus. This connecting piece may be unscrewed for replacing the small rubber ring in the compression valve.

In use, the uterine cannula is inserted into the uterus and, while being held with one hand, the outer screw cannula is slid forward and gradually screwed into the external os, until sufficiently snug to be airtight.

If traction is needed on the cervix to slide the inner cannula past the internal os, the screw cannula may be utilized for this purpose by screwing it into the cervix after the inner cannula has reached the internal os. The latter may then be passed into the fundus.

Finally, the lock joint is closed by turning it down in a clockwise direction. Insufflation or uterosalpingography may then be proceeded with as usual.

REFERENCE

- (1) Colvin, E. D.: AM. J. OBST. & GYNEC. 37: 168, 1939.

LEIOMYOMYXOSARCOMA OF THE UTERUS

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(From the Gynecological Service of the City Hospital)

THE case detailed below is reported because of the interesting clinical history, the comparatively rare pathologic entity (as evidenced by a review of the literature of the last twenty years), and the fact that this apparently highly malignant tumor was restricted as to its metastatic manifestations.

A 50-year-old, colored female was admitted to the Gynecological Service of City Hospital on May 3, 1940, with a chief complaint of pain and swelling of the abdomen of eighteen years' duration. The patient first noticed a painful mass in her abdomen eighteen years ago and went to another institution to seek treatment. There she was told that she had heart trouble and did not need an operation. From that date she had seen no physician until two months prior to admission. During this interval, the patient had only slight discomfort and constipation. The last menstrual period was two years ago with no bleeding since. A single gravidity resulted in a miscarriage. There was no further relevant history.

Physical examination revealed a chronically ill, colored female of about 50 years of age. The head and neck were essentially negative. The lungs showed slight dullness to percussion in the left lower chest anteriorly and posteriorly and occasional fine râles at both bases. Both diaphragms were raised. The heart was normal in size, the rate was regular but somewhat rapid, and no murmurs were heard. The abdomen was enlarged beyond that of a term pregnancy and filled with a hard irregular mass that extended from the pelvis to under the costal margin. The mass seemed to originate in the pelvis, was fixed, and not tender. There was no demonstrable free fluid. Above the umbilicus and just under the skin, a circumscribed solid mass about 15 cm. in diameter and relatively freely movable was palpated. Vaginal examination revealed normal external genitalia and perineum. No cervix could be palpated as it was apparently effaced. The whole pelvis was filled with the mass.

The laboratory data were as follows: Blood count: Hb, 9 Gm. (Sahli); red blood cells, 3.86 m.; white blood cells, 24,000; differential, 66 per cent segmented neutrophils, 19 per cent stab forms, 15 per cent lymphocytes. Blood sedimentation time: 12 minutes. Urinalysis: negative. Blood Wassermann: negative.

Various diagnoses were made by the several members of the staff; mine was mammoth fibroids with sarcomatous degeneration. Due to the fact that the tumor could not be definitely demonstrated to be an inoperable malignancy, it was decided to do an exploratory laparotomy.

On May 8, 1940, under cyclopropane anesthesia, the abdomen was opened. A large solid mass was found which arose from the uterus. There were numerous smaller tumors, ranging in size from that of a pea to orange, which were attached to the peritoneum, the mesentery, and the omentum. Another very large mass was found in the upper abdomen. This tumor adhered firmly to the under surface of the diaphragm and liver. The uterine mass, which extended well above the umbilicus, was removed. During this procedure the patient went into shock and a transfusion was immediately started. Since the patient's condition was becoming increasingly grave, 2,000 c.c. of normal saline were placed in the abdomen, and it was immediately closed. In spite of the transfusion of 900 c.c. of blood, the patient failed to recover from the shock and died four and one-half hours later.

The following is a summary of the findings at autopsy and the pathologic report. On opening the abdomen it was found to be filled with a tremendous tumor which was round in shape and reached from the diaphragm to the pelvic brim. It was not attached to any organ but adhesions bound it to the serosal membranes of the peritoneal cavity, and it was removed with some difficulty. Section of the mass revealed a central cystlike cavity and many areas of necrosis and hemorrhage. There were whorls of pale whitish tissue which were solid and homogeneous in character. The parietal peritoneal surfaces were studded with small metastatic nodules. Larger nodules (1 to 3 cm. in diameter) were noted along the aorta. The heart, lungs, abdominal parenchymal and hollow organs,

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

IMMEDIATE PUERPERAL DEATH*

AN ANALYSIS OF 318 MATERNAL DEATHS OCCURRING WITHIN
TWENTY-FOUR HOURS OF THE DELIVERY OF A VIABLE INFANT

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THE formation of local committees on maternal welfare throughout the United States has resulted in the accumulation of much data on puerperal deaths. These data offer material which previously was not available for study. Among the facts noted is the time interval between fetal birth and maternal death. Maternal death within twenty-four hours of delivery of a child, at or beyond the twenty-eighth week of gestation, has been selected for this study. The material is analyzed to show the frequency, causes, preventability, and avoidable factors in such deaths.

The data were compiled from the records of the Committee on Maternal Welfare of the Philadelphia County Medical Society from 1931 to 1938, inclusive. This committee classified maternal deaths as:^{1, 2} (1) true maternal deaths, in which pregnancy, labor, or the puerperium is directly responsible for the death, (2) deaths in which other diseases are the primary cause, but pregnancy, labor, or the puerperium is a contributory cause, and (3) those deaths in which pregnancy or labor had no effect (nonobstetric).

The true maternal deaths and those in which the obstetric condition was a contributing factor were analyzed by the committee to determine if the death was preventable or not preventable. If it was preventable, the avoidable factors were noted. The opinion of the majority of the committee was the final decision in the classification of the death, in assigning its preventability and in the noting of the avoidable factors.

Frequency.—During this eight-year period, 1,587 women who were pregnant or in whom the pregnancy was recently terminated died in Philadelphia. Excluding abortion and ectopic gestation, 937 (59 per cent) patients died after the pregnancy had advanced to or beyond the twenty-eighth week of gestation. Three hundred and eighteen pregnant women died within twenty-four hours of the delivery of a viable child. Consequently, in this study, a maternal death within twenty-four hours of the delivery of a viable child occurred once in every five maternal deaths due to all causes, and once in every three maternal deaths in which the pregnancy had advanced to, or beyond, twenty-eight weeks.

Causes of Death.—Of these 318 patients, 26 (8 per cent) (Table I) died from nonobstetric causes. The remaining 292 (92 per cent) (Table II) died with pregnancy or labor as the sole cause or a contributory factor in the death. This latter group of deaths are classified as obstetric deaths.

Of the 292 obstetric deaths, 262 (90 per cent) died solely as the result of obstetric causes; in the remaining 30 (10 per cent), pregnancy or labor was a contributory factor in the death. Of the 292 obstetric deaths, it was noted that the three most common causes of death, postpartum hemorrhage (19.5 per cent), shock (16.4 per cent), and eclampsia (11.6 per cent), accounted for 47 per cent of the deaths while the next three most common causes, placenta previa (9.2 per cent), placenta abruptio (9.2 per cent), and ruptured uterus (6.1 per cent) accounted for 24 per cent of these deaths.

*Read at a meeting of the Obstetrical Society of Philadelphia, May 2, 1940.

A HARD RUBBER PLAQUE FOR ANCHORING AND FACILITATING THE REMOVAL OF RADIUM APPLICATIONS TO THE BODY OF THE UTERUS

BROOKE M. ANSPACH, M.D., PHILADELPHIA, PA.

THERE are certain disadvantages in retaining radium with cervical and vaginal packing. It favors accumulations of blood or endometrial debris in the endometrial cavity and the possible passage of minute fragments into the tubes.

When the vaginal outlet is relaxed, the pack and the rubber tubes containing the radium may be displaced by an increase of intra-abdominal pressure from vomiting, coughing, or sitting up in bed.

As the bulk of the pack interferes with urination, catheterization often becomes a matter of necessity. One may use a retention catheter but fussy patients are annoyed; it may predispose to cystitis, and there is some pain during its removal.

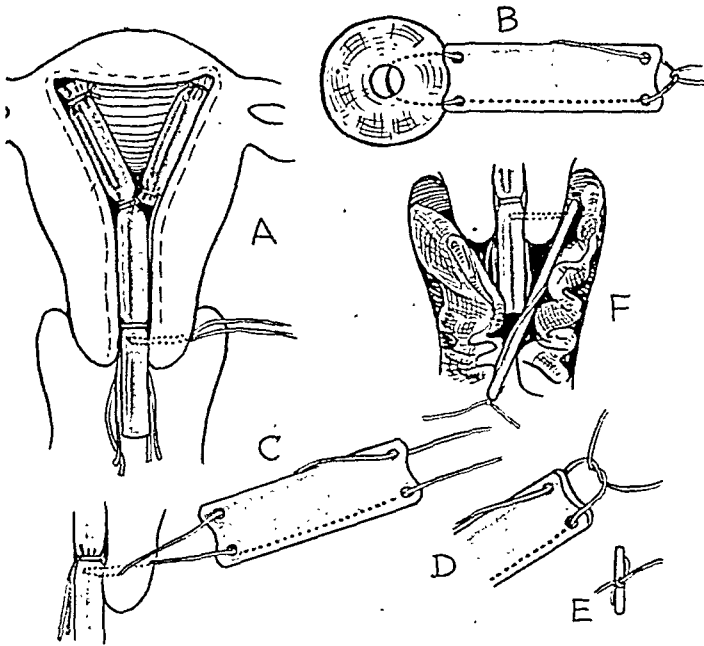


Fig. 1.—A, The radium in platinum capsules with walls 1.5 mm. thick is placed in black rubber tubes singly or in tandem. One to three capsules are used; the larger number is used in carcinoma of the fundus. The capsules are suitably disposed to cover as much of the uterine interior as desired. B, C, D, The anchoring thread is a fish-line passed first with a sharp needle through the wall of the cervix into the cervical canal, then with a thin round point needle through the rubber tubing in the midline below the radium, and finally with a sharp needle back to the vaginal surface of the cervix about a half inch from the point of introduction. D, E, The ends of the thread are carried through the perforations in the plaque and tied as indicated. F, The position of the plaque and the packing at the end of the procedure are shown.

To overcome these difficulties, for several years I have used with much satisfaction the hard rubber plaque herewith illustrated. It ensures free drainage from the uterus and does away with anything more than a few folds of gauze. The radium is securely held in place so that the patient may sit up or even get out of bed to empty the bladder.

Catheterization is avoided; the patient's local discomfort is reduced to a minimum. The anchoring thread is readily accessible at the vaginal outlet and removal of the radium is made easy.

twenty-four-hour deaths assignable to the physician's error. One hundred and thirty-two (40 per cent) of the 318 deaths that occurred within twenty-four hours of the delivery of a viable child were due to preventable errors upon the part of the attending physician.

COMMENT

Any improvement in maternal mortality rates comes through decreasing the preventable deaths. In this study the records indicate that the avoidable factors ascribed to the attending physician are frequently the result of his lack of knowledge and skill. It is not too much to ask the physician who accepts the responsibility of obstetric care to be fully acquainted with normal pregnancy, labor, and the puerperium. He should remember that a very large percentage of his patients will be normal. Familiarity with the normal will make recognition of the abnormal relatively easy. If he is unable to cope adequately with the abnormalities, he should seek expert advice and help. In this connection a factor rather frequently noted was the performance of difficult operations, notably version and extraction, by physicians inadequately trained in such procedures. Hospital surroundings make many men too bold and quick in their decision to terminate labor operatively. The records show that, in quite a few of these patients, operative work was performed when the time of election had not arrived, or had passed. Several patients had operative procedures performed after long trial labors without adequate preoperative rest and preparation. They were dehydrated, acidotic, and tired. Fatal shock frequently followed.

Many patients in this series did not have the type of prenatal care which brought them to their delivery in the best possible physical condition. Quite a few showed anemia, and many of the cardiac patients had insufficient rest periods in the latter months of pregnancy. Potential toxemia patients failed to have sufficient number of prenatal visits, and those who had actual toxemia had little or no observation. X-ray study of the pelvis was infrequently done in patients with cephalopelvic disproportion. X-ray pelvimetry is of great value in borderline cases, and is recommended before labor.

The number of deaths due to post-partum hemorrhage indicates that the third stage of labor calls for more careful management, particularly in regard to awaiting the complete separation of the placenta before attempts at expulsion are made. The manual removal of the placenta was occasionally incomplete. Quite a few patients died from post-partum hemorrhage because of poor contractile power of the uterus following operative delivery in cases of uterine inertia. Atony of the uterus should be suspected in all patients manifesting varying grades of inertia, and preparations made to combat it following the second stage of labor. Several patients died following the exhibition of large doses of pituitary substance which caused deep cervical lacerations or rupture of the uterus. Many of the patients dying of the various forms of ante-partum or post-partum hemorrhage did not receive the benefit of blood transfusions. This procedure was too little utilized, especially in the early years of the study. The larger hospitals' blood banks and the more general procurement of donors preoperatively have ameliorated this situation to a certain extent, and transfusion always should deserve prime consideration.

SUMMARY

1. Three hundred and eighteen (33 per cent) of 937 maternal deaths after the twenty-eighth week of gestation occurred within twenty-four hours of delivery.

2. Two hundred and ninety-two (92 per cent) of these 318 deaths were obstetric deaths.

3. Of the 292 obstetric deaths, 71 per cent were caused by postpartum hemorrhage, shock, eclampsia, placenta previa, placenta abruptio, and inversion of the uterus.

4. Of the 292 obstetric deaths, 171 (58 per cent) were judged preventable.

5. The preventability of these 171 obstetric deaths were assigned to the physician in 132 (77 per cent) and to the patient in 39 (23 per cent).

6. Since 12,000 women die from all puerperal causes in each year in this country, should a similar ratio of preventability obtain as occurred in this study, the elimination of the immediate puerperal preventable deaths from the standpoint of the physician's education or skill would save 1,000 lives annually.

TABLE I. NONOBSTETRIC CAUSES OF DEATH

DISEASES	NUMBER
Total	26
Pneumonia (lobar and bronchopneumonia)	7
Valvular heart disease	4
Acute cardiac dilatation	3
Rheumatic and chronic endocarditis	3
Acute pulmonary edema	2
Miscellaneous, one each of the following: chronic rheumatic fever, acute yellow atrophy of liver, influenza, purpura hemorrhagica, epilepsy, cerebrospinal meningitis, acute toxemia	

TABLE II. OBSTETRIC CAUSES OF DEATH

DEATHS WITH PREGNANCY OR LABOR AS SOLE OR CONTRIBUTORY CAUSE	NO. 292	PER CENT 100.0
True maternal deaths (pregnancy or labor sole cause of death)	262	89.7
<i>Diseases:</i>		
Post-partum hemorrhage	57	19.5
Shock (obstetric, puerperal, etc.)	48	16.4
Eclampsia	34	11.6
Ruptured uterus	27	9.2
Placenta previa	27	9.2
Placenta abruptio	18	6.1
Pulmonary embolism	13	4.4
Toxemia	10	3.4
Inversion of uterus	8	2.7
Sepsis	7	2.3
Nephritis	6	2.0
Pre-eclampsia	4	1.3
Miscellaneous: One each of kidney of pregnancy, vomiting of pregnancy, puerperal sudden death	3	1.0
PREGNANCY OR LABOR CONTRIBUTORY TO DEATH	30	10.3
<i>Diseases:</i>		
Acute cardiac dilatation	5	1.7
Mitral stenosis	3	1.0
Lobar pneumonia	3	1.0
Cerebral embolism	3	1.0
Embolism	2	0.6
Myocarditis	2	0.6
Influenzal toxemia	2	0.6
Miscellaneous: One each of pyelitis, rheumatic endo- carditis, thrombosis in broad ligament (spontaneous) acute myocardial failure, myocardial insufficiency, cerebrospinal meningitis, cesarean section, cardiac decompensation, spinal anesthesia, anesthesia	10	3.4

Preventability and Avoidable Factors.—In the opinion of the analysis committee, 121 (41 per cent) of the 292 obstetric deaths were unavoidable catastrophies. In the remaining 171 patients (59 per cent) of this group, an avoidable factor was judged causative of the death. In the records of the management of these patients, the committee found that ignorance or self-neglect of the patient was the avoidable factor in 39 (23 per cent), while in 132 (77 per cent) there was an error upon the part of the attending physician as the preventable factor. Of this latter group of 132 patients, the physician's prenatal care was inadequate in 10 per cent, and his judgment or/and technique in the management of their obstetric problem was deficient in 90 per cent.

Frequency of Twenty-Four-Hour Preventable Deaths Assignable to Physician.—One hundred thirty-two (14 per cent) of the 937 patients who died after the pregnancy had advanced to or beyond the twenty-eighth week of gestation were

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Labor

Spiller, Violet: Duration of Labour in Primiparae, *Lancet* 2: 733, 1939.

In 1,400 consecutive patients delivered by the vaginal route, all of whom received analgesics during labor, there was a low but definitely positive correlation between the age of the patient and the duration of labor. The average length of labor of patients between the ages of 18 and 39 was 23 hours and 39 minutes. Half of the patients had labors lasting less than 20 hours. In the age group between 24 and 27 years, which represented nearly two-fifths of the total patients, 65 per cent had a shorter than average labor, and half of the patients had labors lasting between 7 and 18 hours.

CARL P. HUBER.

Moir, Chassar: The Occipito-Posterior Positions of the Vertex and Their Complications, *Brit. M. J.* 2: 555, 1938.

A brief discussion of the causes, dangers, and diagnosis of this abnormality is offered. The chief cause of the difficulty is thought to be a maladjustment of the shape of the fetal head to the shape of the birth canal. Unusual postures of the fetus in utero, an increased inclination of the pelvis or a poorly flexed fetal head favor nonrotation. When nonrotation, or malrotation occurs in a large pelvis with a small head, or a deficient perineum, delivery is usually easy. Frequently a mild degree of pelvic contraction accompanies nonrotation. These cases are more difficult to manage.

Radiologic methods of study are new aids in diagnosis. Late engagement of the head, and early rupture of the membranes in the absence of disproportion between the head and the pelvis are signs of malposition. Fetal heart sounds heard in the flank, and peculiar uterine contractions are often present. Labor may be obstructed by an edematous scalp. Vaginal examination is essential and an anesthetic is required in any case of doubt before forceps delivery is undertaken.

The dangers to mother and fetus are grave in this condition. Fetal mortality is high and puerperal sepsis frequent.

F. L. ADAIR AND S. A. PEARL.

Vartan, C. Keith: Cause of Breech Presentation, *Lancet* 1: 595, 1940.

From a review of 969 breech deliveries, the author concludes that it is wrong to teach that the cause of the breech presentation at term is a pelvic anomaly which prevents the head from entering the pelvis. He believes that the cause is the failure of the fetus to undergo a spontaneous cephalic version. Spontaneous version was prevented by an extended attitude of the fetus in 37.3 per cent of the group studied, by the presence of another fetus in 23.6 per cent and by prematurity in 9 per cent. These three factors may account for 70 per cent of breech presentations. In 22.9 per cent of the cases no cause was recorded. Placenta previa was present in only 3.2 per cent and disproportion in only 1.3 per cent, and for that reason neither can be considered as an important etiologic factor. Pelvic tumors, and an abnormally shaped uterus, hydrocephalus, hydramnios, and anencephaly are so rare as to be of little significance in the production of breech presentation.

CARL P. HUBER.

I wish to acknowledge the help of the members of the Committee on Maternal Welfare of the Philadelphia County Medical Society in compiling the records, the aid given by Miss D. Malkiel in compiling the statistics, and the advice and suggestions given by Dr. Douglas P. Murphy and Philip F. Williams in the preparation of the manuscript.

REFERENCES

- (1) Maternal Mortality in Philadelphia 1931-33, P. F. Williams, Philadelphia County Medical Society, 1934. (2) *Runnels, S. C.*: J. Am. Inst. Homeo. 25: 1408, 1932.

250 SOUTH EIGHTEENTH STREET

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MAY 2, 1940

The following case reports and papers were presented:

A Case of Hematuria Complicated by Pregnancy. Dr. Owen J. Toland.

Ovarian Pregnancy, Primary or Secondary? Drs. Bernard Mann, D. R. Meranze, and Benjamin Leff. (For original article, see page 322.)

Immediate Puerperal Death. H. D. Lafferty. (For original article, see page 342.)

MEETING OF OCTOBER 3, 1940

The following papers were presented:

The Emergency Control of Post-partum Hemorrhage: Experience with a Supplementary Technique. Drs. C. C. Briscoe and R. A. Wilson.

Siamese Twins (Thoracopagic) Complicating Triplet Pregnancy. Drs. R. J. McNeil, H. L. Crowther, and N. F. Paxson. (For original article, see page 337.)

Some Cardilogic Factors of Importance in Obstetric Practice. Dr. W. G. Leaman, Jr.

ST. LOUIS GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 17, 1940

The following papers were presented:

Endocrine Factors in Gynecologic Disease. Dr. Willard M. Allen. (By invitation.)

Increased Uterine Response to Pituitrin Following Alkalinization. Dr. Roy V. Boedeker.

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 4, 1940

The following papers were presented:

A Review of 94 Mixed Mesodermal Tumors of the Uterus. Drs. Morris Glass and J. W. Goldsmith. (For original article, see page 309.)

The Toxemias of Pregnancy. Drs. Frank P. Light, D. S. Fettes and N. J. Mazzola.

Iontophoresis in the Treatment of Pelvic Infections. Drs. Charles A. Gordon and A. H. Rosenthal. (For original article, see page 237.)

Local Refrigeration in Genital Cancer. Drs. Charles A. Gordon and Joseph V. Cresci. (For original article, see page 281.)

possess a well-developed secondary center of ossification at the distal end of the femur and usually a smaller secondary center at the proximal epiphysis of the tibia, whereas the cuboid will present in only one-half. Two carpals, the capitatum and the hamatum, the coracoid center and the medial humeral epiphysis will be present in 12 per cent, 20 per cent, and 30 per cent of the cases. This corresponds very well to the chart for development of the human skeleton (to which the authors do not refer) as furnished by Paul C. Hodges, except that in the latter's experience the coracoid usually does not appear until the end of the sixth month of extrauterine life.

They compare these normal cases with 22 infants which were delivered at least fourteen days after the estimated date of confinement. Again the x-rays were obtained on the newborn infants and not upon fetuses in utero. Slightly greater advance in bone development is observed in the postmature group but this is usually in the direction of the presence of those centers of ossification which may be present at term, but are not as commonly observed as the distal epiphysis of the femur and the proximal epiphysis of the tibia. They believe that the size of centers of ossification which are normally present in a term infant is a more reliable criterion of postmaturity than the actual presence of certain other centers of ossification, a conclusion arrived at by members of the Children's Bureau of the United States Department of Labor, who are in the process of tabulating the results obtained by x-rays of more than 1,200 newborn infants from various gestational periods and in different races.

This criterion of postmaturity is not practical for antenatal use and is only relatively sound. The authors do not state the incidence of visualization of the knee joint in utero, but show three reproductions of x-rays which do not prove routinely good intrauterine visualization of the fetal knee joint. It has certainly not been the experience in this country that a high degree of visualization in utero is possible even with special positioning of the patient. But if this were possible, the average error, which is in the neighborhood of 2.0 mm. with our most accurate roentgen methods, would void, for diagnostic purposes, such differences as the authors deal with when a bone diameter measures 5.0 mm. at term and 7.0 mm. in the postmature.

Finally, the authors have not taken into account the racial differences which do exert a definite influence upon bone development in the human being. They show in one of their tables that the female infant is farther advanced in bone development than a male infant of comparable gestational age. X-rays from the Children's Bureau series show a similar advancement in bone age of the negro infant over the comparable white infant. Interestingly enough, the degree of advancement in bone development of the female infant over the male, and of the negro infant over the white, is essentially the same as the authors have found in the postmature over the term infant. Racial differences might well account for the discrepancies which the authors point out in the previously reported charts of skeletal development.

A. L. DIPPEL.

Maizels, Gerald: High Puncture of the Membranes; A Review of 842 Inductions of Labour With the Drew Smythe Catheter, *J. Obst. & Gynaec. Brit. Emp.* 47: 237, 1940.

The author reviews his experience in 842 inductions of labor with the Drew Smythe catheter which enables one to do a high rupture of the membranes, allowing the escape of from one-half to one pint of liquor amnii. With this method one can leave the bag of forewaters intact, thereby lessening the dangers of ascending infection, prolapse of the umbilical cord and dry labor. The method, in general, is that devised by Hopkins (1814).

It was found that if surgical induction is preceded by a routine medical induction a better response is obtained. The patient is allowed to walk about after the rupture of membranes and if labor has not started by the third day the medical induction procedure is repeated, and if that does not succeed a

Crosse, Mary V.: Management of the Frank-Breech Presentation, Brit. M. J. 2: 113, 1939.

In a series of 100 cases the child mortality rate was considerably reduced by using simple methods with no risk to the mother. In the first place, all unnecessary interference was eliminated; and, second, a special effort was made to provide a skilled and sufficient staff of attendants for each breech delivery.

The management of the delivery is kept as simple as possible; there is no interference except fundal and suprapubic pressure, unless definite indications arise. A leg is pulled down only when there is definite delay during the second stage, as the complete breech is a better dilator than the half-breech. In no case was it found necessary to bring down a leg during the first stage of labor. Traction is not used, as this extends the arms and head. Hot towels are not employed, as they obstruct progress and make handling of the infant difficult. In no case has the child suffered from this omission. Forceps are used only when there is difficulty with the aftercoming head. They are, however, always boiled and ready for use in emergency. Episiotomy has been performed in most of the later cases of the series, especially in primiparas, as it reduces pressure on the infant's head and also eliminates risk of a third-degree tear. It is done while the breech is distending the vulva.

The risk of stillbirths in this series was 4 per cent and the risk of neonatal death, 5 per cent.

J. P. GREENHILL.

Goethals, Thomas R.: Management of Breech Delivery, Surg. Gynec. Obst. 70: 620, 1940.

The occurrence of breech presentation as a problem in the management of labor at term may be handled in one of three ways. The obstetrician may convert the breech to a vertex by the maneuver of external version; he may deliver the infant as a breech through the pelvis; or he may elect to perform cesarean section.

From a study of 2,035 pelvic breech deliveries and 58 abdominal cesarean sections in the Boston Lying-in Hospital from 1888 to 1937 inclusive, the following conclusions have been drawn.

1. About 7 per cent of primigravidas with breech presentations at term should be delivered by section.

2. Roentgenographic mensuration of the fetal head in utero has a definite if limited value in helping to diagnose fetopelvic disproportion. The ideal method of making a comparison of the fetopelvic relationship in breech presentation has not yet been determined.

3. The statistics and experience derived in this study indicate that, if delivery through the pelvis is selected as the method of choice, the second stage of labor should be terminated by breech extraction under full surgical anesthesia before the birth of the umbilicus has occurred.

WILLIAM C. HENSKE.

Stampfel and Tscherne: The Radiological Diagnosis of Postmaturity in the Fetus, Ztschr. f. Geburtsh. u. Gynäk. 119: 31, 1939.

The authors set out to determine the normal state of development of the human skeleton by the time of delivery of the term infant, i. e., just which of the usually employed primary and secondary centers of ossification are present when the infant is born previous to nine days after, but not before nine days in advance of the calculated date of confinement. They show two previously reported charts of development of the human skeleton, refer to several others, and point out the lack of uniformity in these.

The experience of the authors with x-rays of 90 term newborn infants, 45 males and 45 females, leads them to conclude that a term infant will always

doses. There is a great individual variation in uterine response to quinine and the amount required to sensitize the uterus to normal contraction impulses is small.

R. J. WEISSMAN.

Sibayama, K., Ogura, S., and Miyata, D.: Fetal Death Due to Quinine, *Sankato Huzinka* 5: 1, 1937.

At the Japanese Red Cross Lying-in Hospital, the authors observed three fetal deaths in a series of 802 cases where labor was induced by means of quinine. In one case the mother had received 0.6 Gm. (9 gr.) quinine, the second mother had been given 0.9 Gm. (13 gr.) and the third mother 1.5 Gm. (22½ gr.) by mouth and 1.5 Gm. by injection within forty-eight hours.

J. P. GREENHILL.

Blomfield, George W.: Administration of Pituitary Extract in the Third Stage of Labor, *Brit. M. J.* 2: 1083, 1938.

Experiments performed by the writer are claimed to show: (a) that there is no danger whatever in giving 1 c.cm. of pituitrin or pitocin during the third stage of labor; (b) that the amount of hemorrhage is not much affected: in the series there was a tendency to a smaller post-partum loss in the pituitrin cases.

It is not claimed that posterior pituitary extract should be given in the third stage as a routine treatment for all cases, nor should control of the fundus or the very watchful care that is necessary at this stage be relaxed, or be replaced by an oxytocic drug.

J. P. GREENHILL.

Emmrich, J. P.: The Prophylactic Intravenous Injection of Posterior Lobe Extract in the Period after Confinement, *München. med. Wchnschr.* 86: 329, 1939.

A study of statistics presented by various observers shows that the number of men who favor the injection is just as large as the number opposed to it, that the effect of the injections cannot be explained entirely by statistics and that even in a large amount of material there are sure to be discrepancies caused by differences in the biologic processes.

Used as a prophylactic, the intravenous injection of posterior pituitary lobe extract as a routine after confinement offers no advantages. Atonies, Credé manipulations, and manual removals occur almost as often as in women who have not had the injection. The differences are very small and lie within the limits of statistical errors.

On the other hand, it is advisable to use the prophylactic injection in selected cases of spontaneous deliveries, in which, as in hydramnios and twins, atonic hemorrhages can be expected as well as in most operative deliveries, especially in those with an insufficiency of labor pains. In these cases a physiologic course of the third stage of labor cannot be expected.

Therapeutically, in atonic hemorrhages this intravenous injection is the treatment of choice, and if used, it should be followed by an intramuscular injection after the delivery of the placenta. The effect of the intravenous injection is limited in duration and a definite relaxation may follow, and this is the reason why it has not come up to expectations.

C. E. PROSHEK.

Corbet, Robert M.: Post-partum Haemorrhage, With Special Reference to Partial Detachment of the Placenta, *Brit. M. J.* 2: 438, 1939.

The paper deals with the mechanism of separation of the placenta, suggesting that the Schultze mode, rather than that of Duncan, is the normal one.

second puncture should be performed on the fourth day when the amount of liquor amnii withdrawn will usually be 6 to 8 ounces.

After high rupture of the membranes, labor begins at various intervals, but 86 per cent of the cases are in labor within four days. This method is considered unsuitable for breech presentation, but the safest for the treatment of disproportion.

The author feels that the results obtained indicate that maternal and fetal mortality rates are not increased, and the maternal morbidity and sepsis are lower than in any other surgical method of induction. The incidence of prolapse of the umbilical cord is not increased.

WILLIAM BERMAN.

Kreis, J.: The Justification of Rupturing the Membranes and Its Relation to Dilatation of the Cervix, Acta obst. et gynec. Scandinav. 19: 52, 1939.

In the opinion of Kreis, effacement and dilatation of the cervix are neuromuscular phenomena accompanied by physiologic or pathologic inhibitions arising in the cervix. The integrity of the bag of waters is either unnecessary or even an obstacle to the functional coordination of the uterine musculature. Premature or early rupture of the membranes with normal progress of labor constitutes a natural correction of an inhibitory disturbance. In unfavorable cases there is unsatisfactory development of the lower uterine segment and rupture of the membranes alone cannot overcome this. Since it is impossible to foretell at the beginning of labor with or without rupture of the bag of waters when disturbances in the lower uterine segment will arise, the author advocates the use of antispasmodics routinely before or after rupture of the bag of waters, regardless of whether this takes place spontaneously or artificially.

J. P. GREENHILL.

Cattaneo, Piero: Clinical Observations on the Treatment of Uterine Inertia, Associated with Premature Rupture of the Membranes, with Quinine-Calcium, Rassegna d'ostet. e ginec. (Naples) 48: 257, 1939.

The author observed the progress of labor in 23 patients who had uterine inertia with early rupture of the membranes. The inertia was treated with intravenous injections of quinine-calcium. The average duration of labor after use of the drug was eight and one-half hours.

The uterine contractions proceed with normal force in some cases of premature rupture of the membranes but in other cases it may be necessary to hasten the labor to save the child. He reviews the literature, German and Italian, and observes that the maternal mortality rate is increased in cases with premature rupture of the membranes. For this reason the author felt justified to use quinine-calcium to effect earlier delivery.

His series of 23 cases includes 10 primiparas and 13 multiparas. All the mothers lived. Two infants were born dead, one of them a monster and the other a macerated syphilitic infant. Forceps were used in 12 cases. The membranes had ruptured prematurely more than twenty-four hours in 11 cases.

The dosage of the drug was: 5 c.cm., intravenously, in 16 cases; 2.5 c.cm. in a case dilated 8 cm. when inertia developed; and 6 to 15 c.cm. in divided doses, intravenously and intramuscularly, in 4 other cases.

CLAIR E. FOLSOME.

Heyrowski, K.: Dosage of Quinine in Labor, Deutsche med. Wchnschr. 66: 576, 1940.

Citing a case of quinine intoxication in which a Werlhof type of purpura appeared, Heyrowski concludes that optimal doses of quinine for the initiation of labor lie in the range of 0.002 Gm. per kilo of body weight. The drug should not be given in excess of 0.1 Gm. per dose and not more than 3 or 4

Cyclopropane was present in the fetal blood in almost as high concentration as in the maternal blood. However, only about half as much nitrous oxide was found in the fetal as in the maternal blood.

Judged by biochemic data, cyclopropane as an obstetric anesthetic would appear to be perhaps less safe for the infant than the clinical appearance of the mother would indicate.

WILLIAM C. HENSKE.

Smith, Clement A.: Effect of Nitrous Oxide Oxygen Ether Anesthesia Upon Oxygenation of Maternal and Fetal Blood at Delivery, Surg. Gynec. Obst. 70: 787, 1940.

Judging by the amount of oxygen reaching the fetus at birth, the data presented indicate nitrous oxide and oxygen alone or combined with ether to be a less satisfactory obstetric anesthesia than ether alone.

WILLIAM C. HENSKE.

Kühnel, P.: The Treatment of Uterine Atony in Labor by Means of the Scalp Forceps, Acta. obst. et gynec. Scand. 18: 466, 1938.

In 14 cases of pronounced uterine atony in which there was a cephalic presentation, the author used a scalp forceps with a weight attached to it. Other methods of stimulating labor pains were tried before this measure was employed. The results were so encouraging that the author recommends this procedure in cases of uterine atony where other measures have failed and the only alternative seems to be a craniotomy. The author also employed weight traction on a scalp forceps in a case of breech presentation.

J. P. GREENHILL.

Rucker, M. Pierce: Kielland Forceps, Virginia M. Monthly 66: 676, 1939.

The author states that the Kielland forceps exert practically no pressure on the baby's head when properly applied. The head can flex and extend and rotate as the birth canal may determine. For this reason delivery can be effected with less force than with any other type of forceps. Rucker on several occasions has been unable to deliver the baby with the axis traction forceps without using unwarranted force, and then, substituting the Kielland forceps, delivered the baby with ease. The classical conditions for forceps applications must be present with the Kielland forceps just as with any other model. To use the Kielland forceps successfully they must be applied according to the technique outlined by Kielland, which emphasizes accurate diagnosis of the position. Because of the ease with which these forceps are applied and the delivery effected, the author states that their chief fault is that one is tempted to use them when indications for forceps application are not present.

EUGENE S. AUER.

Daels and de Backer: Prophylactic Symphysiotomy, Zentralbl. f. Gynäk. 63: 1119, 1939.

The writers advocate prophylactic symphysiotomy. They believe that in certain cases of cephalopelvic disproportion symphysiotomy should be carried out before labor begins when the patient is in good condition and not exhausted as after a hard labor. Such a procedure is without danger and a minor operation. The authors warn against abduction of the thighs in cases of prophylactic symphysiotomy because all they want to accomplish is to increase the diameter of the pelvis only $\frac{1}{2}$ to 1 cm. so the pelvis may yield a little during labor.

J. P. GREENHILL.

Post-partum hemorrhage is divided into 3 classes: (1) Placental site hemorrhage; (2) true atonic hemorrhage, where there is no bleeding until after delivery of the placenta; (3) traumatic hemorrhage, where the bleeding comes from lacerations in some part of the birth canal.

Placental site hemorrhage is said to be caused by failure of the normal mechanism of placental separation, resulting in detachment of part of the placental margin before the central area has separated, with consequent escape of the retroplacental hematoma and loss of its important wedge action. Along the line where partial detachment has occurred, the maternal vessels are held open and continue to bleed, full retraction of the uterine muscle being prevented by the portion of the placenta still attached. There are various causes for this condition such as twins, hydramnios, fibroids, low implantation of the placenta, short cord, ill advised handling of the uterus, and attempts at expressing the placenta before it has entirely separated, morbidly adherent placenta, and prolonged operative deliveries. Some occur without apparent cause. In treatment, where hemorrhage has ceased, supportive measures are indicated before attempting delivery of the placenta, but when bleeding still continues, delivery should be accomplished promptly. The author discusses the Credé method and the manual removal of the placenta, methods of arresting hemorrhage after it has been removed, and the use of the oxytocic drugs in this connection. True atonic hemorrhage and traumatic hemorrhage are dealt with briefly.

FRED L. ADAIR, AND JOHN NEWDORP.

Smith, Clement A.: The Effect of Obstetrical Anesthesia Upon the Oxygenation of Maternal and Fetal Blood With Particular Reference to Cyclopropane, Surg. Gynec. Obst. 69: 584, 1939.

Determinations were made of the oxygen content of arterial and venous blood from women during labor. Similar determinations were made upon the arterial and venous bloods of 3 groups of mothers and their infants at the moment of birth. These 3 groups represented routine deliveries under ether, under nitrous oxide-oxygen, and under cyclopropane anesthesia. In the second and third groups, the amounts of nitrous oxide and of cyclopropane were also quantitatively determined in the maternal and fetal bloods. An attempt was made to correlate the degree of oxygenation of maternal and fetal blood with the type of anesthetic used, and to discover the relationship between fetal anoxemia and the presence or absence of apnea in the newborn infant. The following observations seem significant:

Oxygenation of maternal blood during labor but before delivery an anesthesia was comparable to that observed by other authors for maternal blood at delivery without anesthesia. The arterial blood during labor showed a slight anoxemia.

In general, ether anesthesia produced a definite elevation of the maternal oxygen capacity, and of the oxygenation of maternal venous blood. Under the anesthesia the fetal oxygenation appeared to be satisfactory.

Nitrous oxide, administered with at least 20 per cent oxygen, produced a definite maternal and fetal anoxemia.

Under cyclopropane, the maternal blood showed a pronounced elevation of oxygenation in both the arterial and venous specimens. This is probably not due to the high concentration of oxygen administered with cyclopropane. The blood of infants delivered under this agent was somewhat better oxygenated than those born under nitrous oxide-oxygen. It contained less oxygen than the blood of infants delivered under ether, or that reported in the literature for those delivered without maternal anesthesia.

Pronounced anoxemia in the fetal blood at birth was not constantly accompanied by apnea of the newborn infant, except in babies delivered under nitrous oxide-oxygen. Fetal anoxemia is probably one of several factors which may operate to produce apnea. A surprising degree of fetal anoxemia may be associated with a normal onset of respiration.

Item

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Cleveland, Ohio, by the entire Board from Wednesday, May 28, to Monday, June 2, 1941, inclusive, prior to the opening of the annual meeting of the American Medical Association in Cleveland.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 1, 1941.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reexamination* in Part II must make written application to the Secretary's Office before April 15, 1941.

In accordance with the previously announced plans of the Board, the examinations to be given for the Board's fiscal year 1941-42 (ending with the Part II examination in June, 1942) will be the last for candidates under Group A and B classifications. Applications must be in the Secretary's Office at least 90 days in advance of the announced examination dates, which dates are published in the various medical journals. Following the close of the final date for receipt of Group B applications (October, 1941) and Group A applications (March, 1942) all candidates will be considered in one classification by the Board, thus doing away with the junior and senior groups for examination, and all candidates will be required to take the Part I examination (written paper and submission of case histories) as well as the Part II examination (oral and pathology).

Military service will not affect the eligibility of any candidate so far as the Board requirements regarding limitation of practice are concerned. Military service will under no circumstances be considered as an infringement of any regulations outlined in this Board's booklet.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

This Board will hold its annual dinner for Diplomates, and others interested in the work of the Board, on Wednesday evening, June 4, 1941, at the Wade Park Manor Hotel, Cleveland, Ohio, immediately following the close of the Part II examinations, which will be conducted in Cleveland in the spring, immediately prior to the opening of the annual A. M. A. meeting.

Lundgren, A. T., and Boice, William A.: **Knotting of Umbilical Cord**, Illinois M. J. 76: 451, 1939.

The authors report three instances of true knotting of the umbilical cord, resulting in the birth of stillborn fetuses. They estimate the incidence of this anomaly as about 0.3 per cent. The article quotes the views of various other writers on the etiology, mechanism, and effects of knots of the cord. It concludes with a complete bibliography of the subject as found in both American and European literature.

EUGENE S. AUER.

Dippel, A. Louis: **Hematomas of the Umbilical Cord**, Surg. Gynec. Obst. 70: 51, 1940.

Hematoma of the umbilical cord, excluding its origin from rupture of a large varix or aneurysm of the umbilical vein, is an exceedingly rare complication of pregnancy and labor, occurring about once in 5,500 deliveries at or near term. The great majority of hematomas occur at approximately full term. Essentially one-half of all fetuses whose umbilical cords contain hemorrhagic areas are stillborn. The hemorrhage usually arises from rupture of the wall of the umbilical vein, though occasionally the wall of an umbilical artery ruptures; and rarely does the hemorrhage arise from the capillaries of the fetal end of the funis. The size of the hematomas varies greatly and the majority are located nearer the fetus than the placenta. Maternal complications of pregnancy are neither common nor limited to syphilis and the toxemias. The causes of rupture of an umbilical vessel are obscure and probably several factors enter into the development of a hematoma in each case. Before delivery, the only clinical evidence of the presence of a hematoma of the cord is that of fetal distress or occasionally that of vaginal bleeding.

WILLIAM C. HENSKE.

Friedlander, D.: **A Case of Intrapartum Death Due to Intrauterine Rupture of the Umbilical Vein**, J. Obst. & Gynaec. Brit. Emp. 47: 334, 1940.

The author reports a case of intrauterine death of a fetus in a primipara in whom labor was induced. The cause of the fetal death was due to a rupture of the umbilical vein in utero. The mother's prenatal course had been entirely uneventful, and her serology was negative. She developed some intrauterine infection post partum, and the author suggests that this infection may have been the etiologic factor in the rupture of this vessel.

WILLIAM BERMAN.

In discussing preventability and assigning responsibility, I have followed no rule or formula. I have relied upon my obstetric judgment, my knowledge of the individual case, and whatever experience I might have gained from thirty years of such work. I did not find this analysis an easy task. I do not believe that any two men would get the same answer. From my analysis I have concluded that 52.5 per cent of these deaths were preventable. Lest we jump at conclusions, let me hasten to say that it is not a practical, workable percentage.

The responsibility for these preventable deaths was assigned as follows:

	PER CENT
Hospital doctor	37
Patient	37
Hospital routine	12
Outside doctor	10
Midwife	4

I confess to some astonishment at finding that patient and hospital professional staff share approximately an equal responsibility. However, I think that the largest truly preventable responsibility can be assigned to the hospital doctor. Perhaps I have been overcritical in determining our bad judgment, but if more leniency had been exercised, the figure would still have been too high. If we have such a large reducible factor in our own service where constant effort is made as to supervision and conservatism, it does not seem fantastic to speculate that probably 25 per cent of all colored maternal deaths can be prevented by the improvement of professional care alone. There is, of course, a certain irreducible figure, but so far as our service is concerned, a more constant and intensive supervision of the resident and intern staff would have told a different story.

Errors of commission on the part of the attending staff were relatively rare, errors of omission more frequent. During this period, the resident was given too much responsibility, oftentimes a responsibility requiring the judgment and dexterity of a larger experience. I am inclined to think that residents and interns on colored obstetric services are generally given more responsibility than they are capable of assuming and that this is a real cause for some of the obstetric deaths in colored women.

The preventability and responsibility as assigned to the patient is inaccurate, rather illogical, and requires discussion. A preventable percentage of 37 assigned to the great majority of negro women is an illusion. If we consider the ignorance and the poverty of the Negro race and all of the economic and social complications that go with ignorance and poverty, most of these deaths cannot now be prevented. Indifference is a larger factor than is realized. Many more years are needed to correct fundamental causes.

Granted that there is much room for professional improvement, considerable experience leads me to believe that a more sustained and permanent improvement must have as its background some education of all women.

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PRESIDENTIAL ADDRESS*

SOME REMARKS ABOUT MATERNAL MORTALITY
IN THE SOUTH

JAMES R. McCORD, M.D., ATLANTA, GA.

MATERNAL mortality in the South is high. This high rate is in large part in negro women and in rural white women; those living below even a moderate subsistence level. Many factors make difficult an accurate study of maternal mortality in such women. I have long pondered the real situation. This study is in part an effort to clarify my own thoughts, and to try to obtain an accurate evaluation concerning the high maternal mortality in negro women.

My remarks have as a background the deaths of 97 colored pregnant women. All of these deaths occurred on our obstetric service at Grady Hospital in the city of Atlanta. The hospital is entirely charity and the only one available to a colored population of approximately 150,000. The service has accepted the hospital deaths of all pregnant women. The deaths were consecutive and no corrections were made. Deaths from ectopic pregnancy were not included.

The care of these women was beset with many difficulties, which those of you who have services in similar institutions can accurately evaluate. The complete service rendered these women was not the best. I feel sure, however, that it was much better than the average service received by negro women in the South. One statement can be made without equivocation; it was uniformly conservative. I might say here that the uncorrected mortality rate on our service is 5.6 per 1,000 pregnant women. This includes obstetric and nonobstetric deaths.

*Given at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Excelsior Springs, Mo., September 26 to 28, 1940.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

parently normal when admitted. About one-third of the total number either delivered or aborted on the outside. The causes of death were:

Peritonitis	24
Bacteriemia	9
Bacteriemia and peritonitis	2
Sepsis	5

The fact that one-third of the septic women who delivered in the hospital were operated upon is questionable. There seemed to be a direct staff responsibility of about 12 per cent. Hindsight is better than foresight. Decisions were largely conservative, and if repetition were possible I do not see how they would be materially changed. The midwife and the outside doctor were relatively unimportant in this group. This is because the clinic during 1938 cared for 91 per cent of the colored obstetrics in the city and county. Only 64 live babies were delivered by midwives in 1938. Parenthetically, it is my opinion that, if colored midwives (bad as they are) were abolished under present conditions, colored maternal mortality in the South would immediately increase.

As chief of the service I am most concerned with the fact that I have attributed the primary responsibility for 15 per cent of the septic deaths to our hospital routine. This figure is not an accurate one, nor do I believe it is possible to get an accurate figure. But when apparently normal women enter the hospital and die of sepsis, the only honest conclusion one can reach is that infection probably occurred after admission. I feel sure that such women are a constant worry to every chief of obstetric service in a general municipal hospital. DeLee has said, "The environment has much to do with the causation of puerperal infection." There are general hospitals of good and bad obstetric environment. The lack of improvement of a poor environment is often not any fault of the professional staff. Constant effort, constant supervision, and uniform conservatism in a bad environment cannot prevent the occasional death from sepsis. I am reasonably certain that half of these deaths from sepsis were not preventable with the present economic and intellectual environment of the patients.

Though difficult to prove, I am certain that criminal abortions are rapidly increasing with the urban negress and were the cause of more than a fair percentage of the deaths in this group. There seems to be an idea, rather general, that the negro is a better obstetric risk than the white. She is on the average not a good risk, and is always a likely candidate for infection. There are any number of reasons why this is true. Perhaps the most important is her low resistance caused by an unbalanced and deficient diet. Marked anemia is frequent. The colored obstetric patient is most often stoical and likely to give one a false sense of security. Too often they do not have what it takes for a comeback after a long, hard labor. Superstitions, venereal infections, poor hygiene, and a pernicious environment are influencing factors.

Pre-eclampsia and eclampsia caused 23.5 per cent of the obstetric deaths. It is probable that the rate of death from the two diseases in colored women approximates 35 per cent. It seems worthy of emphasis

The devastating mortality in the South is among the negroes and whites living below a subsistence level. This group does not fare so badly in larger cities with municipal hospitals, but even here, the rate would be considerably lowered by a better economic background. I am unable to see how good obstetric care can uniformly be given these women when such care is measured in terms of professional service alone.

I studied every record in this series, most of them several times. Approximately 30 per cent of these women did not die because of obstetric conditions. The causes of these nonobstetric deaths might be informative.

Uremia	8
Hypertensive heart disease	5
Pneumonia	4
Pulmonary tuberculosis	2
Miliary tuberculosis	1
Pulmonary embolism	1
Chronic nephritis	1
Rheumatic heart disease	1
Carbuncle of kidney	1
Esophageal stricture	1
Thrombosis cerebral artery	1
Peritonitis	1
Ruptured bladder	1
Spinal anesthesia	1

Uremia and hypertensive heart disease were the causes of approximately half the nonobstetric deaths. This was to be expected if one realizes the prevalence of chronic vascular disease in negro women. One wonders how many such deaths incorrectly diagnosed, creep into our southern rates. I realize that with some of these women it is difficult to determine whether pregnancy did or did not hasten death. Proper treatment of several of them would probably have delayed death, nevertheless, they are not obstetric deaths and they falsify our rates. Midwives do approximately 80 per cent of the colored obstetric practice in the South. Information concerning the nonobstetric deaths among these women is not accurate or sound and the statistics reported from such information are misleading and unfair. It is my opinion that 75 per cent of these nonobstetric deaths could not have been prevented regardless of any care that might have been given. Two were probably preventable, two refused advice, and as a result death was hastened, and pregnancy apparently hastened the death of three.

This study, as most similar ones, shows puerperal infection to be the "captain of death" for negro mothers. Nearly 60 per cent of the obstetric deaths were from sepsis. Abortal sepsis accounted for 40 per cent of all deaths from sepsis. Knowing that these were in a general municipal hospital, one immediately begins to question what was wrong and what the real cause behind such a staggering figure. Facts reveal what might be called obstetric helplessness. In 58.5 per cent of the women, the membranes had ruptured prior to admission. An equal percentage had fever when admitted. When first seen half of them had symptoms and signs of infection. Of the others, 25 per cent had definite pathology when first seen. Just one mother out of four who died of sepsis was ap-

In the entire series, 25 per cent had some operation before, during, or after delivery. All but two of the operations were done in the hospital, most of them by an experienced obstetrician after due deliberation. If similar circumstances were repeated few of the procedures would be changed. The total operative incidence of our clinic in 5,000 consecutive deliveries, including abortions, is 3.96 per cent. This figure includes such simple procedures as packing the vagina. However, a critical analysis seemed to show that one-half were preventable, and in one-third the responsibility was placed with our professional staff. It was altogether too evident that more operative responsibility was delegated to the resident than he was capable of handling.

Four placentas were removed manually, two before admission and two after. All patients died of sepsis. Only one out of four of the women operated upon could have been called neglected when admitted. The operations done were:

Manual removal of placenta	1
Supravaginal hysterectomy	3
Breech extraction	2
Secondary abdominal pregnancy	1
Forceps delivery	5
Attempted breech extraction and extraperitoneal cesarean section	1
Hysterotomy and sterilization	2
Internal podalic version	1
Internal podalic version and manual removal of placenta	1
Dührssen's incisions and forceps	2
Craniotomy	1
Therapeutic abortion	1
Spinal anesthesia	1
Cystoscopy	1

Five died from the accidents of pregnancy and labor. One woman with an inverted uterus, who had been delivered by an outside doctor, was dead when admitted. Four died with ruptured uteri. One was cared for on the outside by a doctor, and another by a midwife; both died undelivered. One spontaneous rupture occurred during an apparently normal labor. The intern recognized the complication too late. The last was ruptured during a breech extraction which was done by a resident. This death should properly be assigned to the attending obstetrician.

So the story goes. A veritable hodge-podge of conditions and circumstances. Accurate evaluation seemed almost impossible. We doctors indisputably played an unenviable role. However, there are other problems that should be considered and must be solved before southern maternal mortality rates are comparable with those of other sections of the nation.

What inherent conditions, over which we physicians have no control, are in some measure responsible for our high maternal mortality rates? Webb, in his little book *Divided We Stand*, says, "The North and the South are about the same age. One had its cultural beginning in Massachusetts in 1620; the other made a start at Jamestown in Virginia thirteen years earlier. At that time there was not perhaps any great difference between the people of the two settlements. History and

that 5 of these 16 women died of pre-eclampsia. Seven did not live twenty-four hours after admission, 2 delivered outside and 6 died undelivered. Five delivered spontaneously and 3 had forceps operations. Parenthetically, the diseases were not the indications for the forceps operations. There was one death from pernicious nausea and vomiting. Severe forms of this condition are rare in the negro. The responsibility for the deaths was charged to the staff in 4 instances, to the patient in 9, and to the midwife in 1. Speaking practically and so far as technical care was concerned, at least 50 per cent of these deaths were not preventable. Here again the uncontrollable factor is the patient, the old story of money and environment and the lack of realization of her responsibilities.

I believe that the major factor in southern obstetric mortality is the patient herself. In making this statement I am not trying to shirk professional responsibility. Obstetric mortality reports are likely to be misleading if not compiled from intelligent information. I am inclined to think that too much published data from our section of the country have been gathered without an accurate obstetric background. I do not see how there can be a sustained and substantial improvement in southern maternal mortality without a paralleled economic improvement.

Syphilis has a high incidence in the negro. It has been said that the disease has much to do with the high death rate of colored mothers. I do not believe that this is true. This study helps to substantiate my belief. One or more blood Wassermann tests were done on all but 8 of the women. Twenty per cent were positive, which is about the average figure found in pregnant negroes. Of the last 2,691 Wassermann tests done in our clinic, 21.5 per cent were positive. Only 5 of the 18 women with syphilis had chronic vascular disease, and in 2 of these the vascular disease was a contributory factor in the deaths. The environment that is largely the cause of such a high incidence of syphilis is the major cause of the high death rate in such women. The causes of death in these syphilitic women were:

Sepsis	8
Pre-eclampsia	2
Eclampsia	2
Ablatio placentae	1
Hyperemesis	1
Ruptured uterus	1
Pneumonia	2
Congenital heart failure	1

Hemorrhage was the cause, or was thought to be a contributory factor, in 12 of the 68 obstetric deaths. Two had delivered when admitted. An ablatio placentae, a cervical laceration, and a post-partum hemorrhage were directly the causes of 3 deaths. A more experienced house staff could probably have prevented these. A marginal placenta previa was probably a factor in one death and post-partum hemorrhage perhaps contributed to 9 others. Seven of the 9 died of sepsis and 2 of eclampsia. The loss of blood in our clinic is not measured but estimated. Perhaps hemorrhage was a larger contributory factor than I realized.

Nearly three-fourths of our population depends upon agriculture for a living. The average farm income in the South is \$186 as compared to \$528 elsewhere. Ever since the War between the States, the South has been the poorest section of the nation, despite the fact that nature endowed her with tremendous wealth. One-half of all farmers are tenant farmers, and their income is far below the southern average. Truly they are the peasantry of the United States. The South, with more than half of the farmers in the country, has less than one-fifth of the farm implements. More than half of all southern farmers depend upon cotton alone and cotton has long been an economic hazard. The one-crop system is changing, but the way is long and hard.

The South has less than one-third of the nation's farmland, but has 61 per cent of the land erosion. It loses each year more than \$300,000,000 worth of top soil. Over 22 million acres of once rich land cannot be reclaimed. In the southeast an area as large as South Carolina has been gullied and washed away. It is estimated that in Alabama and Georgia alone 56,500 farm families are living on land too poor to support them under any system of agriculture.

The poorest rural area in America has the greatest number of people. The birth rate of the South exceeds that of any other region. It has a larger percentage of early American stock than any other region in the United States. The native born comprise 97.8 per cent of the population, of which 29 per cent are colored. There are 9 million negroes in the South, rapidly shifting to the larger centers, with probably one-half of them a liability to the community in which they live. Increasing competition for jobs has upset the balance of employment between white and negro, unemployed white people seeking and glad to get jobs heretofore held by negroes.

In the South there are fewer productive adult workers and more dependents per capita than elsewhere in the country. One child in eight, born and educated in Alabama or Mississippi, becomes an asset to some other state. Of all the eminent scientists born in the South, one-half are living elsewhere. Productive middle age groups leave the South in the greatest numbers, tending to make the South a land of the very old and the young.

Hookworm, malaria, and pellagra are real problems and public health work suffers from inadequate tax receipts received from a relatively small percentage of the people. In 1937 the average income from interest and dividends in the South was \$17.55 as compared to \$68.97 elsewhere. Too much of profit from southern industries goes to outside financiers in the form of dividends and interest. State taxation does not reach such moneys. Just as in education, the funds that are needed for public health simply are not available.

These pessimistic and gloomy conditions are not because we want them and not because we are not trying to improve them, however, I believe you will agree with me that such conditions are bound to influence maternal mortality.

Certain economic interests will in time correct many of them, but as Edwin R. Embree says, "There is danger here. What shall it profit the

tradition tell us that the one was Puritan and the other Cavalier; that one was stern and introspective and the other gay and zestful. Perhaps there were some differences in temperament and in inherited tradition, but these may be disregarded in the assumption that had the Puritan been set down in Virginia, he and his children would have become good Southerners, and had the Virginian been set down in Massachusetts, he and his children would as surely have become New Englanders."

The War between the States was devastating to North and South. The South paid a terrific economic price. But great as this was, it was not nearly so harmful as the political carpetbaggers that came later. The North held military and political control of the South until 1876. Today the North is the economic master of the South. This has not happened with the knowledge and abetting of the average northern citizen and no criticism is intended or implied. However the economic unbalance in the nation today is in large part due to this unbalance in the South. Economists say that it must be remedied before an average prosperity can be sustained.

Illiteracy is four times as prevalent in the South as in the rest of the Nation. The average expenditure on education per child is about half that of the country as a whole. To quote Webb again, "Illiteracy is explained by the presence of the negro in the South. But this is only an explanation. The fundamental reason is the lack of means. Beneath the ignorance of the South is not the will to be ignorant, nor an indifference to the advantages of education. It takes money to educate people, to pay teachers, to buy books from northern publishers, and to build the little red schoolhouse so dear to the vote hunting politicians. Let us recall that out of every 100 dollars deposits in banks, the South has less than 10. . . ." The South must educate one-third of the nation's children with one-sixth of the nation's school revenues. Teachers compare favorably with other sections; this in spite of the fact that the average annual salary of a teacher in Arkansas is \$465 as compared to \$2,361 in New York. The total endowments of all its colleges and universities are less than the combined endowments of Yale and Harvard. Our illiteracy is not the result of indifference. The South collects about half as much per person in taxes as does the nation as a whole, but she devotes a larger share of her income to schools. For the South to spend the national average per pupil, an additional quarter of a billion dollars per year would be required. Our economic masters do not pay their share of the cost of southern schools and institutions. The magazine *Look* in the issue of November 21, 1939, said, "For 70 years the South has been the victim of absentee ownership, adverse freight rates and tariffs. Today it is poor and ignorant, not because it wants to be, but because its economic masters have so decreed." Practically all of the money the South spends for insurance, automobiles, groceries, machinery, and other items too numerous to mention quickly leaves for parts unknown.

The average income in the South is half of what it is elsewhere. Comprising 28 per cent of the country's population, the South in 1934 paid about 12 per cent of the total income tax. This was \$1.28 per capita and varied from 24 cents in Mississippi to \$3.53 in Florida.

In the following report, we are not going into the endocrine side of the problem. Since the work of Zondek,¹ Aschheim,² Allen,³ Hartman,⁴ Novak,⁵ and many others, the stimulating influence of the anterior lobe of the pituitary body has to be regarded as a well-established fact. Without this gland and its gonadotropic hormone there is no ovulation. This hormone (prolan A) stimulates the follicular growth.

In some animals (rabbits) who ovulate after cohabitation, a nervous stimulation of the hypophysis takes place which brings about an additional increase of the gonadotropic hormone. Within eight to twelve hours, this leads to the rupture of the follicle. In man and many other mammals who ovulate independent of cohabitation, we have to admit "our ignorance of the exact hormonal factors concerned in ovulation" (Novak⁵).

However, as mentioned above, while lacking details, the fundamentals of the endocrine stimulation of ovulation can be regarded as well established.

Knowing the stimulating influence of the anterior pituitary, we take the rupture of the follicle for granted, not realizing that we are dealing with a mechanical process which requires definite anatomic histologic preparations. In regard to the Graafian follicle, one might feel that this is a cyst which must burst after it reaches a certain size and after the inside pressure becomes too great. If that would be a sufficient explanation, why do other cysts in the ovary, pathologic cystomas, etc., frequently reach the size of a child's head and more, and yet rarely rupture? There must be a histologic difference.

Before reporting our work and the resulting findings, we shall look over the explanation of the mechanism of ovulation in the literature.

In former days when endocrinology was an unknown field, many theories in regard to ovulation were developed.

Pflueger,⁶ in 1859, believed that peristalsis of the ovary was a cause of ovulation. The action of smooth muscle fibers was supposed to bring about the rupture of the follicle. Henle,⁷ however, in 1866, opposed this theory by showing that smooth muscle fibers accompanying major arteries in the ovary never extended into the ovarian stroma. Over sixty years later the muscular theory was revived by M. S. and R. F. Guttmacher,⁸ in 1921, who described smooth muscle fibers in the theca externa of the follicle of swine. There is little histologic evidence for the action of smooth muscle fibers in ovulation. I have never found cells in the theca externa which could be considered as smooth muscle fibers.

Another theory of ovulation regarded active or passive hyperemia as the actual cause (Dahlmann,⁹ Bayer,¹⁰ and others). This idea goes back to the time when it was believed that menstruation and ovulation occurred at the same time, and has since been discarded.

A third theory concerned the possibility of enzymes being able to digest the internal lining of the follicle. Schochet¹¹ felt that there were proteolytic ferments in the liquor of the follicle. But, as pointed out by Smith,¹² there is very little direct evidence for their existence.

The most popular mechanical explanation of ovulation is that the increased pressure within the follicles precipitates expulsion of the ovum.

Koelliker,¹³ in 1874, felt that a sudden increase of liquor production takes place which causes rupture of the follicle. Schaffer,¹⁴ 1920, favored the same explanation.

Robert Meyer¹⁵ has stated that the bursting of the follicle depended upon the relationship between the pressure inside of the follicle and the counterpressure of

South to multiply steel mills and cotton factories simply to become another South Chicago or Pittsburgh river front. What is the benefit of an increase in agriculture if it merely means that two stalks of cotton grow where one grew before, while the farmers starve. Why bigger schools if the children simply learn more rote lessons? Even better health is but little gain unless robust bodies house minds and souls. The South needs material betterment and there is every prospect that she will get it. But the great problem before the region is in getting possession of an abundance of things, to save her own soul. Let us stop pitying ourselves over the ravages of a war which was ended seventy-five years ago. Let us cease mourning over an ancient Golden Age which in reality was never very golden, which at best had but flecks of gilt scattered sparsely over great stretches of poverty, illiteracy and human exploitation. The glory of the South is not in the past but in the future.''

I close with an optimistic prediction that is irrelevant to the subject discussed. This country's God-given heritage of liberty and democracy must be saved, and will be saved, largely by the conservative South.

NOTE: Much of the factual material was obtained from "A Report on Economic Conditions of the South" prepared for the President and from *Divided We Stand* by Webb.

THE THECA CONE AND ITS TROPISM TOWARD THE OVARIAN SURFACE, A TYPICAL FEATURE OF GROWING HUMAN AND MAMMALIAN FOLLICLES*

FOUNDATION PRIZE ESSAY

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THE ovary is the only gland with external secretion which does not have ducts or some permanent outlet. This is one of the anatomic differences between the ovaries and the testes. The latter possess a wide system of tubules and excretory ducts for the spermatocytes, while there is no similar provision made for the excretion of the ova from the ovary.

Ovulation, the delivery of the unfertilized ovum from the ovary, is a mechanical process governed by hormones as is childbirth, the delivery of the fertilized ovum from the uterus. In childbirth, on account of practical needs, the mechanical part of the process has been studied carefully. In regard to ovulation the opposite is the case. We know fairly well the endocrine stimulation, but the mechanical preparation has not been worked out sufficiently. In childbirth, we are dealing with a gross anatomic procedure, which can be readily studied and observed. In ovulation we are dealing with microscopic histologic changes which are difficult to interpret concerning their physiologic function.

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group is found closer to the surface again. There is a typical ascent of the follicles in Group 4. Group 5 is found even closer to the surface than Group 4. Finally, follicles larger than those in Group 5 are visibly protruding over the surface.

How can we explain the descent of the small and the ascent of the large follicles?

The first movement, the descent of the small follicles, is a passive one which is easy to understand, since the ovarian cortex offers more resistance than the stroma. The growing little follicle, therefore, expands toward the hilus, following the line of least resistance.

The second movement, the ascent of the large follicles, is much more difficult to understand, because this movement is an active one which takes place against the resistance of the cortex. How is this brought about?

II. THE ECCENTRIC GROWTH OF THE THECA LAYERS

In Table I, we observed that the appearance of the theca layers coincided with the ascent of the follicles. There are no theca layers in the two smaller groups. They are seen developing in the middle-sized group when the follicles have reached the deepest point in their migration. These theca layers when they first appear in growing follicles are equal at all sides. It is in this group that the formation of liquor sets in, usually in the peripheral pole of the membrana granulosa.

In the two larger groups, a decisive change takes place. There is a *one-sided thickness of the theca interna present at the upper hemisphere of the follicle*. In other words, the theca interna grows eccentrically toward the ovarian surface.

The closer the follicles are found to the ovarian surface the larger they are and the more outspoken is the difference between the wide theca interna at the upper hemisphere and the thin theca interna at the lower hemisphere, at the upper pole being finally eight to ten times wider than at the lower pole. This one-sided thickness of the theca interna is soft, because it consists of crowded, fast multiplying cells with many mitotic figures. The theca externa, on the other hand, is rich in tissue fibers and poor in cells and, therefore, hard. It is wide around the lower hemisphere of the follicle and thin at the upper hemisphere toward the ovarian surface, thus like a goblet keeping the growing follicle from expanding to any other side except where the soft and fast growing theca interna provides an area of lower resistance, which is toward the ovarian surface.

After these facts had been established in human ovaries, the third step was to study the ovaries of other mammalian orders, because we know that there is no important histologic feature in human beings which is not found in animals as well.

III. THE THECA INTERNA CONE

The one-sided thickness of the theca interna toward the ovarian surface was found in human ovaries. The first animal we used in order to study this condition in mammals was the cat. Twenty-two

the surrounding tissue. J. T. Smith,¹² as a result of very interesting experiments reported in 1937, found that there exists an increased osmotic tension in rabbit follicles after injection of pregnancy urine.

There is no doubt that the intrafollicular pressure plays a role in the final rupture of the follicle. To accept this fact, however, as the only explanation of the mechanism of ovulation is as much justified, as to accept the rupture of the membranes and the preceding osmotic tension within the uterus as a sufficient explanation for the mechanism of labor. The increased intrafollicular pressure can be accepted as a fact as proved by Smith.¹² This is, however, the very last phase which immediately precedes the bursting of the follicle.

Our problem is to establish the sequence of events which lead to this final stage. If we examine sections of ovaries of women and mammals, we find invariably the growing follicles deep in the ovarian stroma, while the primordial follicles are found close to the surface. How, then, do the follicles manage to return to the surface? As long as we cannot answer this question, we do not know why they finally rupture.

It has been my endeavor for a period of over eighteen years to study microscopically the histologic changes which culminate in ovulation.

I. THE RELATIONSHIP BETWEEN THE SIZE OF THE FOLLICLES AND THEIR DISTANCE FROM THE OVARIAN SURFACE

The first step in approaching our problem was to find out whether there exists a definite relationship between the size of the follicle and its distance from the ovarian surface.

Six normal ovaries from women between 20 and 41 years of age were cut in serial sections. Sixty-two growing follicles were observed. Their diameter was measured micrometrically as well as their distance from the ovarian surface where they were found nearest to the albuginea. Depending on the size of the follicles, 5 groups were formed (Table I), and the average distance from the ovarian surface calculated for each group. Primordial follicles were not included because they are in a resting stage and always found close to the surface. Follicles over 0.5 mm. diameter were not included, because in this group protrusion of the ovarian surface sets in, which makes measurement of their distance from the surface unreliable. All important changes take place in the groups from a diameter of 0.1 mm. to that of 0.5 mm. Table I shows the results.

TABLE I. SIZE OF FOLLICLE AND ITS AVERAGE DISTANCE FROM SURFACE OF OVARY

GROUP	SIZE OF FOLLICLE MM.	AVERAGE DISTANCE OF FOLLICLE FROM OVARIAN SURFACE MM.
1	Less than 0.1	0.65
2	0.1-0.2	0.82
3	0.2-0.3	1.3*
4	0.3-0.4	0.91
5	0.4-0.5	0.5

*Development of theca.

There is first a descent of the small follicles from the area of the primordial follicles into the ovarian stroma. The longest average distance (1.3 mm.) from the surface is reached in the third group. Here is the turning point. The next

The *smallest follicle with a theca cone* was found in a rabbit (Fig. 1). A group of about twelve theca cells forms a triangular roof on top of the limiting membrane which includes just one row of granulosa cells and the ovum. This follicle has otherwise no theca at all. While the ovarian stroma surrounds this young growing follicle at all other sides as it does the adjacent primordial follicles, a group of cells with bigger nuclei and different in shape and arrangement at the upper hemisphere form a triangular wedge. The axis of this cone points toward the area of the primordial follicles. This is the beginning of the theca cone.

The *next group of follicles* shows the theca cone more distinctly. Fig. 2 illustrates a small follicle of a cat. The granulosa has grown into several layers of cells. The follicle becomes elliptic in this phase because the granulosa grows faster at the upper and the lower poles than at its sides. In the peripheral pole, the formation of the liquor is just beginning. On top of this peripheral pole, the theca

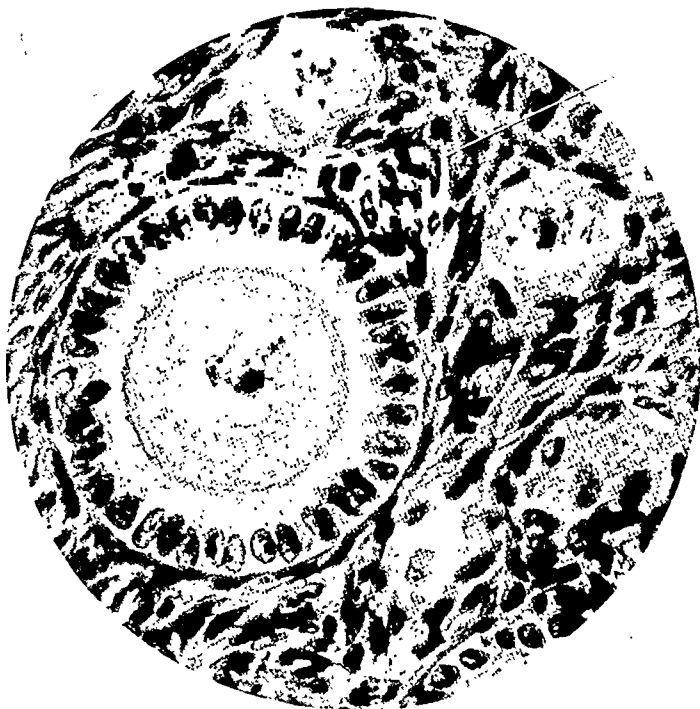


Fig. 1.—Theca interna cone, first stage. Triangular thecal wedge, indicated by line, pointing toward ovarian surface. No theca layers around follicle otherwise, one layer of granulosa cells. Small follicle of a rabbit ($\times 325$).

interna cone is present. There are no theca layers to be found at any other part of the follicle. The theca cone consists of cells in size and shape different from ordinary stroma cells. They show more cytoplasm and big round nuclei. They form a triangular wedge its axis pointing toward the region of the primordial follicles which is the cortex.

Fig. 3 illustrates a small follicle of a rabbit with the same shaped theca interna cone on top of the peripheral pole. It is noticeable that the theca interna is now present all around the follicle. The follicle is larger than that in Fig. 2. The granulosa has multiplied into many more layers. The theca cone is dark because of its crowded cells and nuclei. It pushes the surrounding tissues aside and grows infiltrating toward the area of the primordial follicles, i.e., the ovarian surface.

In the group of *medium-sized follicles*, one observes the effect caused by the one-sided proliferation of the theca interna. These cells infiltrate like the chorio-epithelium of the placenta. They penetrate the ovarian stroma pushing it aside,

cat ovaries were cut in serial sections for a total of 3,000 slides. New unexpected findings made it necessary to go over another set of 9 human ovaries, 3,000 serial sections being made.

After verifying the new findings in this group, the next step was to study ovaries from as many other mammalian species as we could obtain in the pre-estrus or estrus stage, which in larger animals was not always easy.

Together with an apprentice of mine,¹⁹ I examined serially sectioned ovaries of horses, cows, swine, dogs, and rabbits. This represents a total material of 18,381 microscopic slides in four mammalian orders (Primates, Carnivora, Ungulata, Rodentia), which forms the basis of the following findings. Table II gives a survey of the material studied.

TABLE II. MAMMALIAN OVARIES EXAMINED

GENUS	ORDER	MICROSCOPIC SECTIONS NO.
Man	Primates	3,000
Cat	Carnivora	3,000
Dog	Carnivora	1,917
Rabbit	Rodentia	1,423
Swine	Ungulata	3,108
Cow	Ungulata	2,874
Horse	Ungulata	3,059
Total		18,381

The eccentric growth of the follicle and the one-sided proliferation of the theca interna toward the surface were verified in all mammalian orders examined.

The new phenomenon we observed seems to give us the final answer in regard to the ascent of the follicles to the ovarian surface.

The growing follicle develops a sprout much as a seed does. This sprout has a definite "tropism" toward the nearest point of the surface of the ovary. The one-sided proliferation of the theca interna proved to be only the base of the sprout. The eccentric thickness was found by examining serial sections cut in different directions through the ovary. The conelike theca interna sprout is found in serial sections cut at a right angle to the surface. In these slides one finds that the proliferation of the theca interna forms a cone which has a triangular wedge-shaped cut surface, its axis always pointing to the ovarian surface.

I shall now proceed to illustrate the *theca interna cone*, as I have named this structure, in small, medium, and large follicles of various mammals including man. We found the theca cone in all mammalian ovaries which we examined. Since we studied four mammalian orders which all showed the theca cone, we feel entitled to present this feature as typical in the normal histology of the ovary.

In pictures not showing the ovarian surface, the area of primordial follicles will always represent the cortex, in other words, the direction toward the surface.

causing a streamlike adaptation of the surrounding connective tissue by ploughing a path for the expanding follicle. The theca cone provides, at the same time in its rear, an area of lower resistance for the follicle which follows the axis of the theca cone by expanding into the cone as soon as the liquor formation permits the follicle to become cone-shaped itself.

Fast growing tissue rich in cells is soft. The theca interna cone is such a formation. The follicle is surrounded otherwise by dense connective tissue, rich in fibers, and, therefore, hard (theca externa). The growth of the granulosa and the production of liquor requires an outlet. This is provided by the theca interna cone in the direction toward the ovarian surface. We now can explain why in this phase of follicular development the distance between follicle and ovarian surface decreases. The growth of the theca interna toward the ovarian surface is an active infiltrating one. The growth of the granulosa toward the surface is not infiltrating, because it is always surrounded by a limiting membrane, which permits adaptation

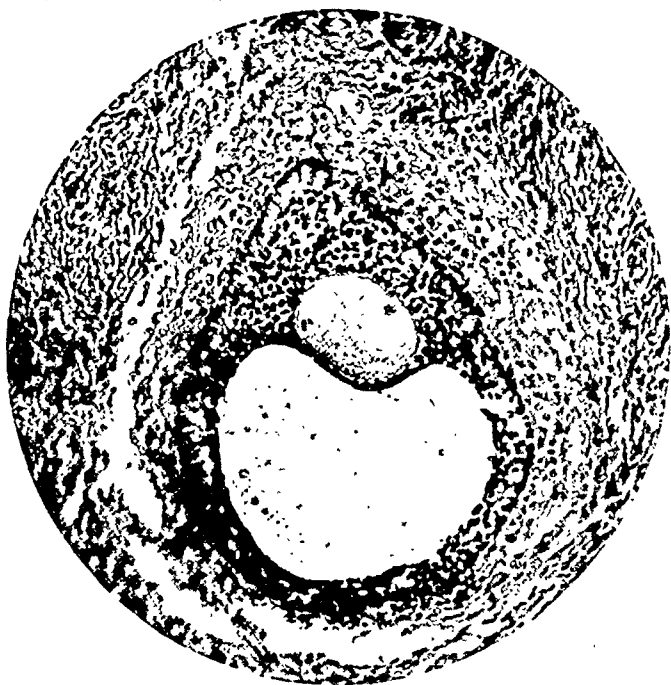


Fig. 4.—Theca interna cone, third stage. Granulosa protruding into theca cone. Appearance of liquor. Human follicle ($\times 160$).

into the cone, but keeps granulosa, liquor, and ovum separated from the theca layers. The adaptation of the follicle proper into the cone is found best when the ovum is located in the upper hemisphere of the follicle. The granulosa grows faster around the ovum than at other parts. It shows more mitotic figures at the cumulus ovigerus. It is, therefore, softer and more adaptable here.

An example is Fig. 4, showing a human follicle with the ovum located in the upper hemisphere. The theca cone is fully developed. *Protruding into the theca cone is the granulosa which becomes cone-shaped itself. The axis of the theca cone and that of the granulosa cone coincide.*

Fig. 5 illustrates the same conditions in a follicle of the cow. The theca interna in both pictures is cone shaped as is the granulosa, which follows the axis of the theca in the direction toward the ovarian surface.

In rabbits and in swine, we found a peculiarity which seems to be an additional help in the ascent of the follicle. The surrounding connective tissue undergoes a marked edematous softening which is more outspoken around the theca cone than at other parts of the follicle.

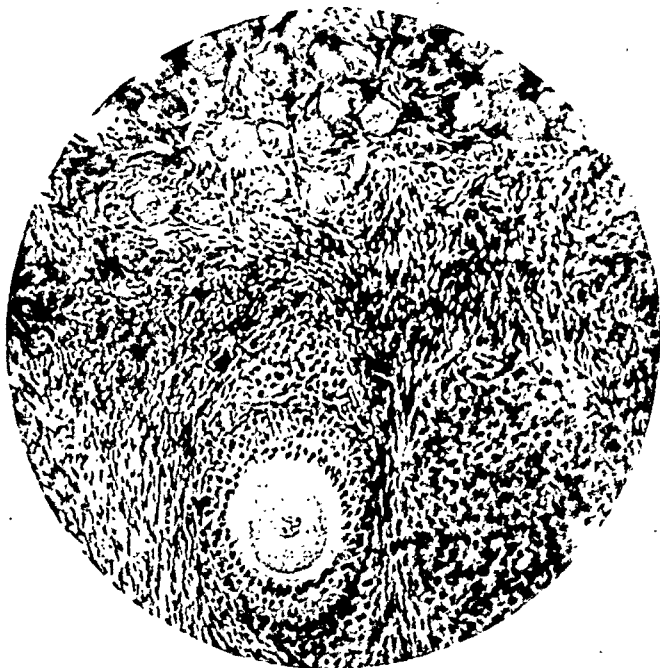


Fig. 2.—Theca interna cone, second stage, pointing toward ovarian surface. No thecal layers around follicle otherwise. Two-three layers of granulosa cells. Small follicle of a cat ($\times 160$).

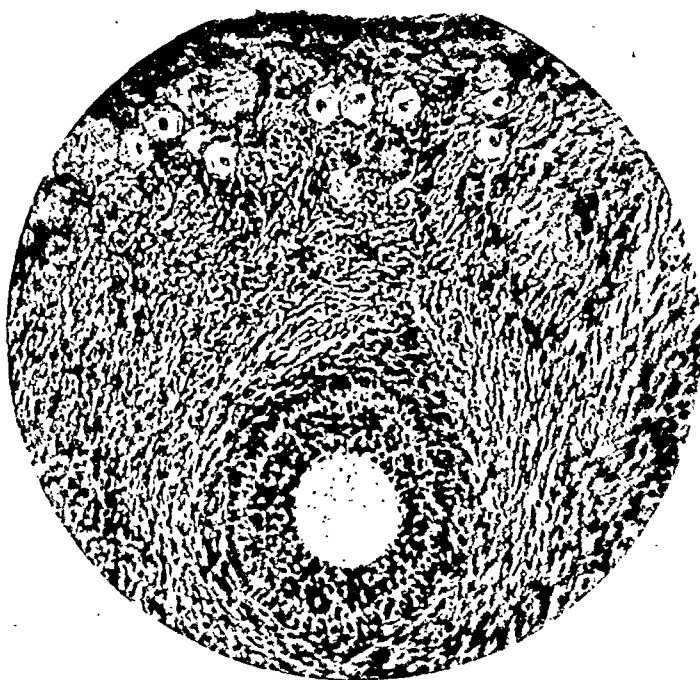


Fig. 3.—Theca interna cone, second stage, pointing toward ovarian surface. Beginning development of theca layers around follicle. Multiple layers of granulosa cells. Small follicle of a rabbit ($\times 100$).

not observe any chemical action, lysis of cells, or destruction of nuclei. The ascent of the follicle seems to be brought about by mechanical changes only, which, of course, are stimulated by endocrines.

Fig. 6 illustrates a human follicle with a fully developed granulosa niche protruding into the theca interna cone. It is noteworthy that both formations have the same axis pointing toward the cortex of the ovary which, in this picture, as always, is recognizable by the area of primordial follicles.

As a typical example of the *group of large follicles*, one can take that of a cat illustrated in Fig. 7. On account of size, only the upper part is photographed. Two atretic follicles lie in the way of the maturing one. One notes with what strength the theca interna wedge is preparing the path for the ripening follicle between the two atretic structures by pushing them aside.

It is not necessary to show the same illustrations for the various mammalian species. The larger the animal, the larger is the ovary, and the more marked is the thecal wedge and the granulosa protrusion into the thecal cone. In small animals, such as mice, the ovaries also are small, and the follicles are near the surface. There is no need for much action of the theca interna, because development takes place right below



Fig. 7.—Theca interna cone and granulosa protruding toward surface of ovary, pushing aside two degenerated follicles. Large ascending follicle of a cat ($\times 60$).

the surface of the ovary. Therefore, I did not see very marked formation of a wedge in the ovaries of mice. In the slightly larger animals, the rabbit for example, the formation of the theca cone was very well developed. Likewise, all the others, without exception, exhibited well-developed formation of the theca cone.

IV. THE ROLE OF THE THECA CONE IN OVULATION

Particularly interesting were the findings in horses, because they gave us the opportunity of determining whether our opinion concerning the significance of the theca interna cone was correct. While in other mammals the ovaries have an entirely free surface which permits ovulation to occur at any place, the ovary of the horse is surrounded by mesovarium, leaving only one little spot free, the ovulatory fossa, where ovulation takes place.

This edema made us wonder as to whether the cells of the theca interna cause destruction or necrosis of the surrounding tissues; in other words, whether the thecal wedge ploughs its way not only mechanically but also chemically, by digesting or dissolving cells of the stroma. By applying the Mallory and Azan stain we tried to determine the presence of such enzymes. The results were negative. I did

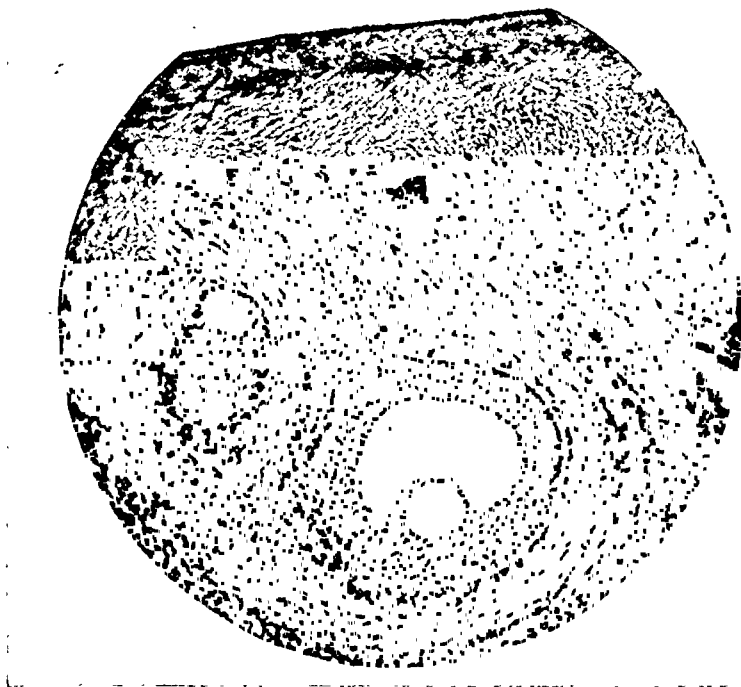


Fig. 5.—Theca interna cone, third stage, and granulosa cone, coinciding axis pointing toward ovarian surface. Streamlined adaptation of stroma. Ascending follicle of a cow ($\times 80$).

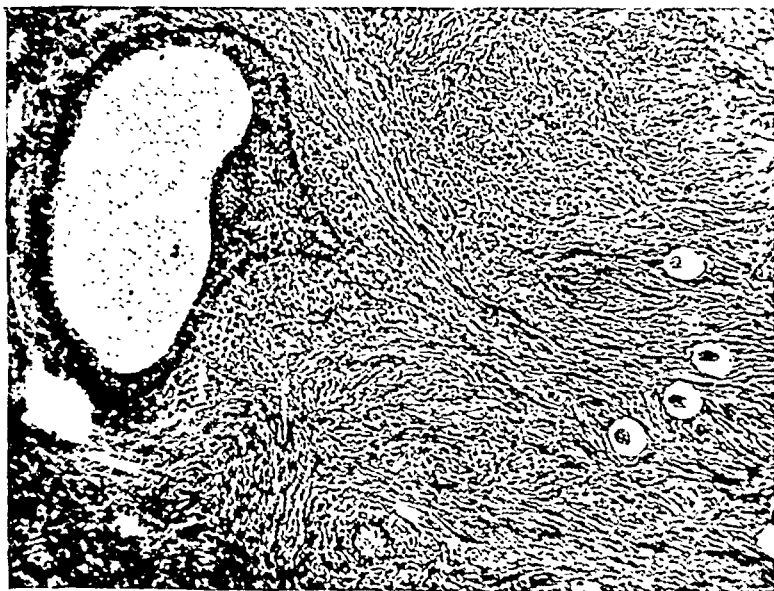


Fig. 6.—Theca interna cone and granulosa protruding in same axis toward ovarian surface. Streamlined adaptation of stroma. Ascending human follicle ($\times 80$).

mammals toward the ovarian surface indicate that this is the mechanism by which the ascensus of the follicles is brought about.

When the ascent of the follicle through the ovarian stroma and the cortex is completed, protrusion commences. The theca interna cone flattens out, forming first a straight line and finally disappearing entirely. Proliferation of the theca plus granulosa ceases, and the membrane between the interior of the follicle and the peritoneal cavity becomes progressively thinner. Circulation on top of the vertex of the Graafian follicle is interfered with by internal pressure. The capillaries do not contain blood cells any more. Atrophy sets in at the stigma. The opening of the follicle takes place in a very smooth manner, almost always without any bleeding.

After ovulation has occurred, the follicle collapses and the walls begin to form the corpus luteum. One cannot confuse the theca interna cone of intact growing follicles with the changes of the theca interna in follicular degeneration if one observes the following differences:

1. *The theca interna cone is present only at one point of the follicle which is always the vertex of the peripheral hemisphere* and closest to the free surface of the ovary. The transformation of the theca in degenerating follicles is observed at all sides.

2. Within many cells of the theca interna cone are *numerous mitotic figures*, seen on high power of magnification (hyperplasia). Among the cells of the theca interna in degenerating follicles almost no mitotic figures are seen; instead the change is one of hypertrophy, owing mostly to infiltration of fat.

3. The cells of the *theca interna cone* form a *solid closed formation*. Only the uppermost cell groups are occasionally surrounded by connective tissue fibers. The cells of the luteinized theca are arranged in groups throughout by septa of connective tissue.

4. Finally, if there is any doubt, *examination of the ovum and the membrana granulosa* always will make evident whether we are dealing with an intact follicle or a degenerated one.

V. GEOMETRIC CONSIDERATION AND PHOTOGRAPHS OF THE THECA CONE IN THE LITERATURE

After the theca interna cone and its significance for the ascent of the follicles have been demonstrated in human and mammalian ovaries, the question arises as to why a typical histologic process such as found in all the mammalian orders examined has not been discovered previously in an organ thoroughly investigated for many generations.

A simple mathematical consideration may explain the situation (Fig. 9).

The cut surface of a sectioned cone appears triangular in shape only if the section passes through the apex of the cone and if its axis coincides with that of the cone, represented by line *I*.

If sections through a follicle are parallel to the ovarian surface, represented by line *II*, we obtain Fig. 9, *b*. All layers of the follicle appear equal on all sides. The thecal wedge would not show in any serial sections containing the cavity of the follicle.

If sections are made obliquely through the follicle, represented by line *III*, we obtain Fig. 9, *c*; this would show only the one-sided thickness of the theca interna and not the wedge. This would hold true only for part of the sections.

In all other mammals studied the theca interna cones grow divergently toward the nearest point of the ovarian surface. In horses we found the theca interna proliferating convergently toward the ovulatory pit, thereby giving evidence that the theca cone has the special function of bringing the follicle up to that part of the ovarian surface where the ovum can enter the peritoneal cavity.

Fig. 8 illustrates a medium-sized follicle of a horse. The theca interna cone is fully developed. The granulosa is protruding into the cone in a very distinct manner, indicating the direction the follicular expansion is going to take. The axis of this cone plus granulosa protrusion is pointing toward the ovulatory pit. This was verified by going over the entire series of sections.

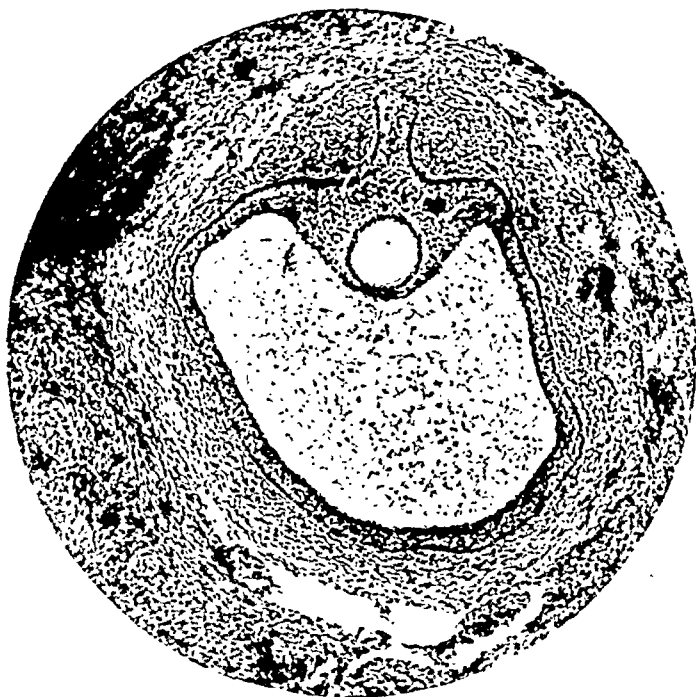


Fig. 8.—Ascending follicle of a horse. Theca interna cone and granulosa protrusion following the cone axis ($\times 60$).

Fortunately, we were able to prove the convergent growth of horse follicles and their theca cones, by showing a photograph of two growing follicles in one microscopic section. Horses ovulate rarely and the incidence of twins is less than in man. It is, therefore, hard to get horse ovaries in the pre-estrus stage, and it is even harder to find two growing follicles close together in one microscopic slide. We felt, however, that we should not stop before finding this combination, because it should be regarded as the final proof that the theca cone has the task of bringing the follicle up to that part of the ovarian surface where ovulation can take place.

The convergent growth of the thecal cones toward the ovulatory pit in horses and the divergent growth of the thecal cones in all other

as a peculiarity in rabbit follicles. The tropism of the theca cones toward the ovarian surface in this picture is evident, since the ovarian surface is visible.

I mention the photographs found in the literature in order to explain that the theca cone is not hard to find after knowing of its existence and significance.

VI. THE THECA CONE AS A TEST FOR GONADOTROPIC HORMONES

After presenting the theca cone and its role in ovulation as a typical feature in the normal histology and physiology of human and mammalian ovaries, the question arises as to whether this knowledge may be of any practical value in our clinical work.

The presence of gonadotropic hormones is indicated by their follicle-stimulating influence. Preparations of gonadotropic hormones are tested by their faculty to stimulate follicular rupture and corpus luteum formation in infantile female animals. In these tests (Aschheim-Zondek test in mice and Friedman test in rabbits) hemorrhage occurs within the follicles. This bleeding is unphysiologic. As mentioned above, normal ovulation occurs without hemorrhage. We know that we are dealing with unphysiologic amounts of gonadotropic hormones if we obtain hemorrhage.

In regard to the diagnosis of pregnancy, we are not interested as to the quantity of hormones the test animals may require for normal ovulation. In regard to the treatment of human beings, however, the quantity of gonadotropic hormones plays an important role. The work of Davis and Koff¹⁶ indicates that the preparations made from pregnant mare's serum are able to stimulate ovulation in man.

Ovulation with hemorrhage means overdosage. We need a test indicating various degrees of follicular stimulation, not only the final stage of follicular rupture. Here may be a place for the theca interna cone as a test for gonadotropic hormones.

The theca cone is found in actual growing follicles only. It is never present in primordial follicles. It is not found in resting follicles if there is such a stage at all. It disappears as soon as degeneration sets in. In other words, it is a sign of actual development of a follicle. It, therefore, may be useful as a test for the presence and quantity of gonadotropic hormones.

We have started animal experiments to determine the time necessary for the theca cone to develop and the time required to bring the follicle to the ovarian surface under normal and artificial stimulation. The results may give us a more detailed picture in regard to the dosage of gonadotropic hormones necessary to obtain physiologic follicular growth and ovulation.

SUMMARY

This paper is a report of microscopic work done over a period of over eighteen years (1921 to 1940). It presents the "*theca interna cone*" and its tropism toward the ovarian surface as a new feature in the normal histology and physiology of the ovary. The theca interna cone

If the sections are made perpendicular to the surface of the ovary, we obtain various outlines of the follicle. A section through line *IV* would look like Fig. 9, *d*. We may visualize the eccentric growth of the theca interna, not the wedge.

*Only if the section is perpendicular to the surface of the ovary and passes through the apex of the cone represented by line I is there a chance to obtain a cut surface showing the triangular shape of the wedge of the theca interna (Fig. 9, *a*).*

This is the reason why we discovered the eccentric growth of the theca interna first. It could be observed more easily than the wedge. The latter could be demonstrated only under favorable conditions. The chance of missing it, even in studying serial sections, is hundreds of times greater than the chance of finding it. This very fact made it necessary to examine a considerable number of ovaries cut in serial sections from various mammalian orders before we were convinced that we were dealing with a typical physiologic process in the normal histology of the ovary in human beings and mammals.

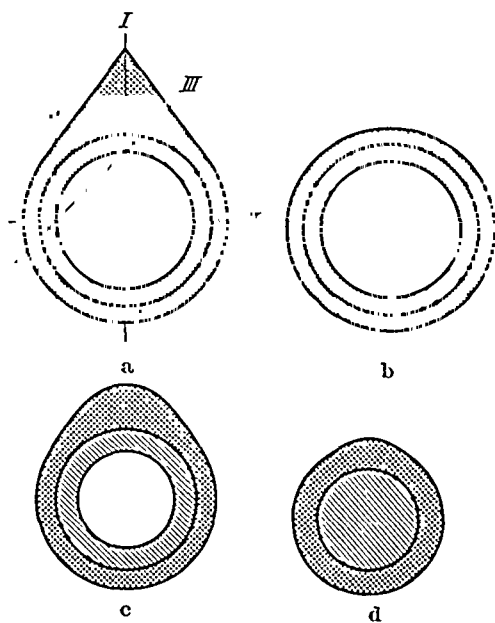


Fig. 9.—Schematic outline of follicle with theca interna cone. Figures *a*, *b*, *c*, and *d* are obtained when follicle is cut following lines *I*, *II*, *III*, *IV*, respectively.

In going over the literature, we found that the theca cone has been photographed and published by other authors who did not realize they had something of importance in their pictures.

First, I have to confess that I am guilty myself. In one of my early papers I pictured a small growing human follicle with a pointed triangular theca interna cone, not realizing that I had the answer to my problem right there (Fig. 3 in reference 17, p. 184).

Recently, I found in B. Zondek's book¹ (page 21), in Fig. 5 which illustrates a human ovary, a small growing follicle with a perfect theca interna cone, pointing toward the area of the primordial follicles.

In J. T. Smith's paper,^{12b} I found another photograph showing theca cones in two rabbit follicles. His Fig. 2, in a very distinct way, illustrates not only the theca cones in both growing follicles but also the edema which we described above

the reason it has not been found before in the ovary, an organ which has been studied by many research workers for several generations.

6. The theca interna cone is present in actually growing follicles only. It disappears as soon as degeneration takes place. It, therefore, can be used as a test for gonadotropic hormones. Rupture of the follicle is useful as a qualitative test, but, if combined with hemorrhage, shows overdosage of gonadotropic hormones. The theca interna cone can be useful as a quantitative test, showing the various degrees of stimulation before ovulation occurs. It, therefore, should become useful for determining the physiologic dosage and timing.

Figs. 1, 3, 5, and 8 are photographs from specimen observed with Erika von Moellendorff, at Paul Strassmann's Clinic, Berlin.

Figs. 2, 4, 6, and 7 are photographs from specimen observed at Paul Strassmann's Clinic, Berlin.

This work was done: (1) in the Pathologic Institute of the University of Freiburg, Germany (1921 to 1922);¹⁷ (2) in the Frauenklinik of Prof. Dr. Paul Strassmann, Berlin, Germany (1922 to 1932);¹⁸ (3) at the University of Berlin, Germany (1932 to 1936);^{18, 19} (4) at the Mayo Clinic, Rochester, Minnesota (1936-1938);^{20, 21} (5) at Houston, Texas (1938 to 1940).²²

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- (19) Von Moellendorff, E.: *Ibid.* 160: 278, 1935.
- (20) Strassmann, Erwin O.: *Proc. Staff Meet., Mayo Clinic* 13: 433, 1938.
- (21) *Idem*: *Surg. Gynec. Obst.* 67: 299, 1938.
- (22) *Idem*: *J. A. M. A.* 113: 1898, 1939.

functions as a pathmaker for the ascent of the growing follicle to the ovarian surface. It, therefore, is an integral part of the mechanism of ovulation.

The findings are based upon over 18,000 microscopic serial sections of ovaries in four mammalian orders: Primates (man), Carnivora (dog, cat), Rodentia (rabbit), Ungulata (horse, cow, swine), and illustrated by photomicrographs showing small, medium, and large follicles of various species.

1. The diameter of human growing follicles and their distance from the ovarian surface were measured micrometrically. Corresponding to the size, five groups of follicles were formed, and the average distance of each group from the ovarian surface was calculated. It is shown that in the early stages of follicular growth, up to a diameter of 0.25 mm., there is a descent of the follicles from the albuginea toward the hilus, and that there is an ascent of the larger follicles back to the surface. This ascensus begins with the appearance of the theca layers.

2. Examination of the theca layers in serial sections shows that their growth is an eccentric one. There is present a one-sided thickness of the theca interna, rich in cells, toward the ovarian surface, which in large follicles is from eight to ten times wider at the upper pole than at the lower pole toward the hilus. The theca externa, on the other hand, rich in connective tissue fibers, is wide around the lower hemisphere of the follicle and thin at the upper hemisphere toward the ovarian surface. Thus, the theca externa, like a goblet, keeps the follicle from expanding to any other side except to the surface of the ovary.

3. In serial sections cut perpendicularly to the ovarian surface, it is found that there is not only a one-sided blunt thickness of the theca interna but a wedge-like "theca interna cone" with a triangular cut surface which always points to the nearest part of the ovarian surface. This theca cone possesses a tropism toward the surface like the sprout of a seed and plows the path for the follicle by active infiltrating growth through the stroma and albuginea. The follicle proper follows the line of least resistance provided by the theca cone. The granulosa protrudes into the cone, frequently adopting the shape of a cone itself, the axis of which always coincides with the axis of the theca cone.

4. The theca cone is found in all mammalian species examined, including man. In all mammalian species with a free ovarian surface, the theca cones grow divergently toward the next point of the ovarian surface. In horses where the ovaries are surrounded by connective tissue, the theca cones grow convergently toward the only free spot, the "ovulatory pit." This proves that the theca cone fulfills the purpose of bringing the follicle to that part of the ovarian surface where ovulation can take place.

5. Geometric considerations show that the theca interna cone can be demonstrated as a triangular-shaped wedge only in serial sections which are cut perpendicularly to the ovarian surface and which run through the apex of the cone. Sections cut in any other direction will never reveal the theca cone as a wedgelike formation. This must have been

"statistics show that in an unselected group of cases in which operation is advisable and is performed by a member of the visiting staff of most accredited hospitals, the mortality rate associated with subtotal hysterectomy is about 4 per cent, and 6 per cent for total hysterectomy." He reports, however, a mortality of 0.9 per cent in 766 subtotal hysterectomies at the Mayo Clinic in a five-year series and a personal mortality of 0.76 per cent in 784 hysterectomies, 196 of which were vaginal hysterectomies with a mortality of 0.51 per cent. Smith³ also reports a mortality below 1 per cent for subtotal hysterectomy at the Evanston Hospital, 0.5 per cent for all hysterectomies, and 0.8 per cent for the subtotal operation.

A six-year survey, which forms the basis of our study, is shown in Table II. It includes all the ward and private patients of the Gynecological services of the Elizabeth Steel Magee Hospital and St. Francis Hospital in Pittsburgh, for the six-year period from May 1, 1934, to May 1, 1940. These operations were performed by 36 surgeons, including the residents. There were 1,640 hysterectomies and 1,464 of these were subtotal hysterectomies, with 28 deaths or a mortality of 1.91 per cent. Included also are 116 total hysterectomies with 5 deaths or a mortality of 4.31 per cent. Sixty vaginal hysterectomies were done with 2 deaths or a 3.33 per cent mortality. The gross total mortality for all cases is, therefore, 2.31 per cent.

TABLE II. TYPE OF HYSTERECTOMY AND MORTALITY

TYPE	NUMBER		DEATHS		PER CENT	
	AUTHORS' CASES	TOTAL SERIES	AUTHORS' CASES	TOTAL SERIES	AUTHORS' CASES	TOTAL SERIES
Supravaginal	442	1,464	2	28	0.45	1.91
Total	53	116	4	5	7.5	4.31
Vaginal	19	60	0	2	0.0	3.3
Gross totals	514	1,640	6	35	1.16	2.13

Out of the total series of hysterectomies, 514 were done by the authors in consecutive, unselected, private and ward cases (Table II); 442 of these were subtotal hysterectomies with 2 deaths or a mortality of 0.45 per cent. We also did 53 of the 116 total hysterectomies with 4 deaths or a mortality of 7.5 per cent. Nineteen vaginal hysterectomies of the 60 performed were our own, and we had no deaths. Therefore, out of 514 cases our gross mortality is 1.16 per cent.

Of the entire series, there were 1,344 cauterizations preceding hysterectomies, or 82 per cent of all cases, though most of them were in the subtotal group, and of these there is a mortality of 1.1 per cent. In the subtotal group, there were 196 cases without cauterization. Thirteen of these patients died, a mortality of 6.5 per cent. The mortality of the cauterized cases was 1.18 per cent. Therefore the mortality percentage in subtotal hysterectomy was five and one-half times as great in the noncauterized as in the cauterized cases.

The diagnoses for the entire series are listed in Table III and represent pathologic reports in all but the mechanical defects. They are presented with the frequency of their occurrence given in percentages. From the table, it can be seen that the occurrence of fibroids, metritis, malignancies, prolapse, and endometriosis total 100 per cent, and the remainder of the diagnoses listed in some measure contributed to the technical difficulties met with in a series of this sort. The number of patients with inflammation is fairly high, there being salpingitis or tubo-ovarian abscess in 39.4 per cent. Cervicitis was found in 76 per cent of the patients.

Some authors (Greenhill,⁴ Schmitz,⁵ Fullerton and Faulkner,⁶ and Farrar⁷) emphasize the dangers of appendectomy or removal of the adnexa in addition to hysterectomy. In Greenhill's⁴ series, the mortality was eleven times as frequent as when the uterus alone was removed. This has not been true in our experience. We do appendectomy almost routinely. In fact, we start below and do everything that we feel is necessary for the patient's future welfare and to prevent

DEEP CAUTERIZATION OF THE CERVIX*

A FACTOR IN REDUCING THE MORTALITY OF HYSTERECTOMY. A SIX-YEAR SURVEY

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HYSTERECTOMY is one of the more common gynecologic operations, and a most useful one, so that every effort should be made to reduce the mortality and morbidity to as low a rate as possible.

There has been much discussion as to the relative merits of subtotal and total hysterectomy, and which operation is preferable in benign conditions. Formerly total hysterectomy had been reserved almost entirely for malignant disease, but in the last fifteen years or more, total hysterectomy has been strongly advocated in some clinics for benign conditions of the uterus, largely because of the hazard, present and future, offered by the infected cervix.

TABLE I. MORTALITY ASSOCIATED WITH SUPRAVAGINAL HYSTERECTOMY
IN VARIOUS CLINICS

	NO. OF CASES	MORTALITY PER CENT
Schmitz	3,129	2.1
Pearse	1,900	1.7
Read and Bell	1,739	2.1
Newell	1,307	3.8
Siddall and Mock	1,141	2.6
Greenhill	1,408	4.6
Amreich	1,253	1.6
Fullerton and Faulkner	609	4.4
Faulkner	653	2.3
Counseller	487	1.9
Mathieu	472	1.9
Danforth	304	0.28
Samuels and Edlavitch	303	2.6
Fletcher Shaw	232	3.05
Masson	217	1.8
Burch and Burch	166	4.2
Dupertuis and Zollinger	755	1.6
Total	16,165	2.5 Average

MORTALITY

Among 16,147 cases reported by 17 authors (Table I) the average mortality was 2.5 per cent for subtotal hysterectomy. Newell and Scrivener,¹ in a review of the literature for a five-year period, found that in 14,280 subtotal hysterectomies reported, there was a minimum mortality of 1.2 per cent and a maximum mortality of 4.7 per cent. In 5,223 total hysterectomies there was a minimum of 1 per cent and a maximum of 7.9 per cent mortality. Masson² states that,

*Read at the Fifty-Third Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Excelsior Springs, Mo., September 26 to 28, 1940.

Further analysis of the deaths of the entire series is contained in Table V. Embolus is the chief cause of death (28.6 per cent), with peritonitis as second offender (21.9 per cent). Shock was the factor in 6 per cent. In Schmitz's series, 25.6 per cent of the deaths were attributed to shock. Fullerton and Faulkner⁶ and Mathieu and associates⁸ listed shock and hemorrhage as the cause of death in 11.6 per cent and 20 per cent of their fatal cases. In our personal series, there were no deaths from shock or hemorrhage. This may be due to our efforts to anticipate and prevent shock by using blood transfusions early in the operation in handicapped patients, or when a severe operation is expected. We had one death from embolus. There were no cases of postoperative intestinal obstruction. Twenty-five per cent of the deaths were in colored patients, although only 13.5 per cent of all the patients were colored.

In three of the four deaths in our own group of total hysterectomies, the operations were performed for carcinoma of the fundus and the patients all presented serious problems from the standpoint of surgical risk and the local conditions of the pelvic organs. The other patient had a fibroid of the cervix, and she is classified as a cardiac death. Pneumonia and cardiac causes are given for the first three. This represents by far the highest mortality for any six-year period, and it is our high mortality in this group that raises the mortality of total

TABLE V. ANALYSIS OF DEATHS

CAUSE	NUMBER OF DEATHS				PER CENT
	SUPRA-VAGINAL	TOTAL	VAGINAL	TOTALS	
Embolus	7	2	1	10	28.6
Peritonitis	8	0	0	8	21.9
Shock	6	0	0	6	17.1
Cardiac	3	1	0	4	11.4
Pneumonia	1	2	0	3	8.6
Carcinomatosis	2	0	0	2	5.7
Thrombophlebitis	0	0	1	1	2.8
Septicemia	1	0	0	1	2.8

TABLE VI. FIVE PRINCIPAL COMPLAINTS

	NUMBER	PER CENT
Pain or discomfort	1,199	73
Bleeding	914	56
Urinary	387	24
Tumor	266	16
Leucorrhea	621	38

TABLE VII. ADDITIONAL PROCEDURES

	NUMBER		PER CENT	
	ALL CASES	AUTHORS' CASES	ALL CASES	AUTHORS' CASES
Cauterization of cervix	1,344	452	82	88
Amputation of cervix	23	12	1.4	2.3
Appendectomy	726	244	44.2	47.5
Oophorectomy {Unilateral	560	193	34.7	37.6
Bilateral	423	79	25.8	15.4
Salpingectomy {Unilateral	355	134	21.6	26.1
Bilateral	746	218	45.5	42.4
Plastic {Anterior	126	43	7.7	8.4
Posterior	260	82	15.8	16.0
Dilatation and curettage	402	64	24.5	12.4
Drain used	446	184	27.2	35.8
Transfusion	248	76	15.1	14.8

TABLE III. DIAGNOSES

	NUMBER	PER CENT
Cervicitis	1238	76
Fibroids	849	52
Metritis { Chronic metritis	526	32
{ Fibrosis uteri		
{ Chronic subinvolution		
Salpingitis	602	36
Tuboovarian Abscess	45	2.7
Ovarian cyst	85	5.2
Cystocele	130	6.7
Rectocele	221	13.5
Prolapse	56	3.5
Endometriosis	148	9
Carcinoma { Cervix	14	0.85
{ Fundus	41	2.5
{ Ovary	25	1.6
Other malignancies	5	0.3
Dermoids	15	0.9

subsequent operations. Each surgeon must know his own limitations in regard to this policy and every surgeon must be cautious about extra procedures in the handicapped patient. Ovarian tissue is preserved as frequently as possible.

The complications associated with the cases operated upon with the above diagnoses represent fairly satisfactory results. Table IV shows the complications and the frequency of their occurrence. It will be noted that of the few operative complications injury to the urinary bladder occurred twice and ureteral fistula occurred once. There were no known injuries to the bladder or ureters in our own series. Postoperatively wound infections, cystitis, and distention were the chief concerns, and the latter two were rather infrequent.

Out of the 442 subtotal hysterectomies done by the authors, there were 2 deaths. One followed an operation for large myomas with adherent adnexa. She had early distention, rapid pulse, and vomiting, and died of a peritonitis or intestinal obstruction. The other death in this group was in a 68-year-old patient with a carcinomatosis, in whom a palliative procedure was undertaken to relieve pain and bleeding. She died on her sixteenth postoperative day from a hemorrhage of the bowel which originated in a penetrating metastatic lesion in her colon. If we may be allowed to correct our subtotal hysterectomy mortality in view of this case, it would then be 0.23 per cent.

TABLE IV. COMPLICATIONS (INCLUDING DEATHS)

	NUMBER		PER CENT	
	ALL CASES	AUTHORS' CASES	ALL CASES	AUTHORS' CASES
Infected wound (not including sinus from drain)	145	33	8.9	6.4
Cystitis	85	31	5.2	6.0
Ileus	53	6	3.2	1.2
Pelvic abscess	21	2	1.3	0.38
Phlebitis, leg	20	7	1.2	1.3
Peritonitis	12	1	0.73	0.19
Pulmonary embolus	11	1	0.7	0.19
Intestinal obstruction	2	0	0.12	0
Pneumonia	11	2	0.7	0.38
Pelvic thrombophlebitis	4	0	0.25	0
Hemorrhage	3	0	0.18	0
Evisceration	4	1	0.25	0.19
Atelectasis	8	2	0.5	0.38
Injury to bladder	2	0	0.12	0
Injury to ureter	1	0	0.06	0

of physicians. In reoperating on these patients, it is found that many of the cervixes are riddled with cysts that are often not evident until deep incisions with the cautery blade are made, and mucus and mucopus evacuate.

We practice deep cauterization of the cervix followed immediately by laparotomy and subtotal hysterectomy. The supravaginal amputation is made low down near the attachment of the sacrouterine ligaments, usually leaving only a rim of cervix. The incision crosses the cauterized and sterilized cervical canal, coning slightly with the knife so as to be able to approximate noncauterized tissue in suturing the cervix. In this method the cervical mucosa is destroyed, the canal is sterilized, hysterectomy is made safer, and future trouble with the stump is practically eliminated. To cauterize or cone out the cervical canal from within the abdomen is not sufficient, for erosions and cysts of the portio cannot be destroyed in this manner.

Treatment of the cervix with the cautery after hysterectomy, as advocated by some surgeons, robs the technique of hysterectomy of one of its most valuable features, namely, preliminary sterilization of the cervical canal. And furthermore, posthysterectomy cauterization may lead to injury of the bladder or bowel which has been placed over the cervical stump.

Formerly, we cauterized only the cervixes that did not seem to be normal. However, it was observed that some cervixes, which looked normal at the time of subtotal hysterectomy, were found to be markedly inflamed on later examination. This is probably the result of circulatory changes in a glandular structure which predispose to infection. It may be the explanation for the reports of carcinoma developing in a normal cervix after subtotal hysterectomy, for we doubt if carcinoma ever develops in a really normal cervix. Masson² has made the same observation and states, "It is known that cervicitis is a very common sequel to subtotal hysterectomy. In more than 500 cases, cervicitis with leucorrhea was sufficient to require treatment after subtotal hysterectomy. In many of these there was no history of leucorrhea before the body of the uterus was removed."

For the last fifteen years, preliminary to subtotal hysterectomy, we have cauterized practically every cervix whether it appeared normal or not. In some clinics the cervix is cauterized and permitted to heal before subtotal hysterectomy is done. This

TABLE VIII. AGE INCIDENCE

AGE RANGE	ALL CASES	AUTHORS' CASES
15-19	6	3
20-24	30	7
25-29	120	47
30-34	297	96
35-39	381	106
40-44	381	119
45-49	242	69
50-54	98	31
55-59	42	18
60-64	26	9
65-69	12	6
70 and over	5	3

TABLE IX. COMPLICATING CONDITIONS ASIDE FROM OR ASSOCIATED WITH THE OPERATIVE INDICATION

	NUMBER		
	ALL CASES	AUTHORS' CASES	
Tuboovarian abscess	45	16	
Pyosalpinx-hydrosalpinx	46	6	
Adhesions	188	88	
Carcinoma	{ Fundus	41	19
	{ Ovary	25	8
	{ Cervix	14	2
Diabetes	18	6	
Tuberculosis	14	5	

hysterectomy in these two hospitals to 4.31 per cent for this period, for the other surgeons had only 1 death in 59 cases, or 1.7 per cent mortality. In the previous six-year period, we had one death from total hysterectomy.

There were 19 vaginal hysterectomies with no deaths in our personal series. The vaginal hysterectomies were done only for third degree prolapse, and many of these were in quite elderly patients.

ROLE OF INFECTION

Infection plays an important role in the mortality of hysterectomy, total or subtotal. Infection is a factor in the occurrence of phlebitis, embolism. In Greenhill's⁴ series, 50.8 per cent of the deaths were due to peritonitis and 13 per cent due to embolism. In Schmitz's⁵ series, 46.2 per cent were due to peritonitis and 3.8 per cent to embolism, and in Mathieu's⁸ series, 40 per cent were due to peritonitis. Dupertuis and Zollinger⁹ attribute 9½ per cent of their deaths to wound infection (*B. welchii*) and 28½ per cent to pulmonary embolism. It is very likely that some of the postoperative pneumonias after hysterectomy are secondary to pelvic infection. Therefore, it is evident that if infection could be much reduced or eliminated the mortality and morbidity of hysterectomy would fall markedly.

Some degree of infection of the cervix is present in the great majority of cases in which hysterectomy is done. Cleansing of the vagina, no matter how meticulous, will not eliminate this infection. Some advocates of total hysterectomy contend that postoperative complications such as pelvic cellulitis, phlebitis, embolism, and peritonitis are more frequent after subtotal hysterectomy as it is usually done than after total hysterectomy. Newell¹⁰ states that this is partially explained by the fact that the infected cervix is cut across in subtotal hysterectomy. Goodall¹¹ also attributes it to mucosal disease of the cervix, and cites the frequent incidence of secondary hemorrhage and parametritis following trachelorrhaphy and amputation of the cervix as further proof of the danger of cutting and suturing the infected cervix. For many years we have felt that the cervix is the principal source of postoperative infection after hysterectomy and have advocated deep cauterization as the best method of sterilizing the cervix preliminary to hysterectomy.

TECHNIQUE

In 1924 the senior author¹² published the technique of deep cauterization of the cervix, and our method of subtotal hysterectomy was published in 1926.¹³ The method consists of single or multiple biopsies of the cervix, dilatation of the cervical canal, cauterization of the canal up to the internal os with Downes cautery blade, and then deep, closely placed radial incisions at the external os to extend beyond and beneath the zone of erosion and infection. The purpose of this procedure is to destroy completely the infected cervical mucosa and glands. The extent and depth of the cauterization depends on the extent of the erosion and cystic condition in the cervix. Each radial cut with the cautery blade varies from ⅛ to ¼ inch in depth. One should aim to cauterize too deeply rather than too superficially. In the subsequent care of the patient, stricture can be disregarded, for when hysterectomy and cauterization are combined, the cervix can be permitted to heal with obliteration of the canal. The serious results of cauterization of the cervix, such as cellulitis, peritonitis, etc., which are stressed by some authors, are due in most instances, we believe, to incomplete cauterization, thereby leaving a zone of infected glands beneath the cauterized tissue. Deep cauterization is preferred because sections of the cervix show that the inflammatory process is frequently deep seated, and that it is necessary to cauterize deeply in order to eliminate it. In practicing deep cauterization, some of the shortcomings of superficial cauterization are disclosed that are not generally known. In cervices that have been cauterized superficially, sections taken immediately afterwards or after healing has taken place, reveal too frequently, that the deep glands have not been destroyed and that they are sealed in by the healing process and extensive cyst formation may result. There are many opportunities to observe this today, as superficial cauterization is done so generally in the offices

We do not imply that cauterization of the cervix is alone responsible for the results of this series. It is only one factor. The other factors are:

1. Careful preoperative estimate of the patient's handicaps and the institution of adequate measures to overcome them, such as blood transfusion, not only in the anemic patients but in those who are less able to withstand operative trauma and loss of blood, especially when a difficult operation is anticipated; blood transfusion started at the beginning of the operation and not after the patient begins to show some degree of shock.

2. An incision large enough to give good exposure so that one can reach down to meet the pathologic conditions rather than to drag them up. We have seen surgeons almost lift the patient from the table in their efforts to bring the uterus above the incision. An alert anesthetist can detect too much traction.

3. Expeditious work in the abdomen commensurate with thorough surgery. In abdominal surgery every minute after the first hour is important so far as the postoperative recovery is concerned.

4. Insertion of a sheet of rubber tissue to cover the raw, oozing surface that cannot be peritonized without too much time and trauma. This is done in order to prevent postoperative obstruction and the formation at times of inflammatory exudate from low grade infection in the blood and serum that will accumulate if no exit is provided.

All of these factors help to lower the mortality but an infected cervix adjacent to a pool of blood or serum in the pelvis increases the danger of complications, and these can be avoided by adequate preliminary care of the cervix.

Up to 1938 the late Dr. R. R. Huggins and the senior author had performed 2,525 subtotal hysterectomies. We know of no case in which cancer developed in the remaining stump in this series, of which 506 were contacted in a follow-up study. There is no doubt in our minds that chronic infection is a causative factor in cancer of the cervix. Meigs¹⁸ and Masson² both estimate the incidence of cancer in the cervical stump as 1 per cent. Levin¹⁷ states that 2 per cent of all women, if followed to their death, will develop cancer of the cervix. If these percentages were applied to the original Huggins and Cashman series of 2,525 hysterectomy cases since 1914, there should develop 25 to 50 cancers of the stump. We know of none. In such a series it may be that occasionally an incipient cancer, too small to be even suspected on gross examination, has been destroyed by cauterization in the stage which Schiller designates as the primary or superficial and Martsloff the covert stage of cancer of the cervix. It is our belief and experience that a cervix healed and free of infected mucosa after cauterization is no more liable to develop cancer than the surrounding vaginal mucosa.

Total hysterectomy at the Magee and St. Francis Hospitals is reserved almost entirely for cancer of the fundus, cancer of the adnexa, and the occasional cervical fibroid. Our subtotal operation is almost a total hysterectomy, as only a small portion of the cervix is left behind. In the majority of cases, perhaps, the removal of this small portion would add but little to the technical difficulty. But in the remainder, as in the

is done to eliminate the danger of peritonitis following cauterization of the cervix and immediate hysterectomy. In our experience, this danger has been greatly exaggerated. In fact, we feel that there is no method other than cauterization at the time of operation that so certainly sterilizes the cervical canal. The cauterized cervix opens into the vaginal canal and the microorganisms that appear later in the slough are saprophytes, and there is less danger of peritonitis than if the infected cervix with its pyogenic organisms is left in place.

For the benign conditions requiring removal of the uterus, we prefer subtotal hysterectomy combined with cauterization of the cervix rather than total hysterectomy, for the following reasons: (1) There is no distortion of the vaginal vault and dyspareunia is thereby prevented. (2) It is a simpler operation and therefore applicable to all cases and adaptable to all hands. (3) The infected cervix is adequately cared for in all cases. (4) We have been able to keep the mortality well below 1 per cent in our own series. (5) The end result is a noninfected, smoothly healed cervix, and no subsequent surgical treatment of the cervical stump for inflammation or newgrowth has been necessary in our series.

DISCUSSION

The advocates of total hysterectomy are correct in maintaining that a subtotal hysterectomy which leaves an infected cervix, or one that becomes infected subsequently, is an incomplete operation. But many of these surgeons do total hysterectomy in *selected* cases, and subtotal hysterectomy in handicapped patients and in technically difficult cases, with the result that in the latter group no treatment of the cervix is carried out, and the patient is left with an infected cervical stump. For the past six years our mortality for subtotal hysterectomy has been below 1 per cent in consecutive, unselected cases and the cervix has been adequately cared for by deep cauterization in all but three cases. There has been no necessity for subsequent treatment of the cervical stump for inflammation or neoplasm. As long as that situation prevails, we see no reason for changing to total hysterectomy. We have grave doubts as to whether we could keep the mortality rate at that level if we applied total hysterectomy routinely to a similar series which includes all of the physically handicapped, the adipose, the inflammatory and the technically difficult cases.

Murphy¹⁵ reports the marked increase in bladder and ureteral injuries and in the incidence of pyelonephritis since the more general adoption of total hysterectomy in the Women's Hospital in New York, even in the hands of experienced operators. The ureteral injuries in his series were 0.24 per cent in subtotal hysterectomy and 1.6 per cent, or 6½ times as many, in total hysterectomy. Acute postoperative pyelonephritis was three times as frequent in total as in subtotal hysterectomy in his series. Leventhal¹⁶ in reporting on ureteral injuries states that the larger proportion of these cases occurred after 1930, when the staff began to perform total hysterectomy more often for conditions which were formerly treated by subtotal hysterectomy.

Fullerton and Faulkner⁶ reported a 2½ per cent incidence of peritonitis among the postoperative complications of total hysterectomy. Thirty-three and one-third per cent of the deaths after total hysterectomy reported by Newell and Scrivener¹ were due to peritonitis. Deep cauterization is advisable even if one is contemplating total hysterectomy, for it is the most effective method of sterilizing the cervix which is to be removed through the abdomen. In the instance where a total hysterectomy has been planned, but once inside it is decided to do subtotal hysterectomy, the cervix will have been cared for by this preliminary treatment, and a diseased stump will not be left behind.

focus of infection, or as a likely site for malignant transformations. With ample time for preoperative attention, the majority of damaged or infected cervixes can be converted to a healthy state. If the cervix is to be left, the vaginal surface of the portio must be completely epithelized, and the endocervical canal free from infection and inflammatory products. It, therefore, seems much more logical to restore such a cervix to normal by office treatment before the hysterectomy, rather than simultaneously to create a large slough from the extensive cauterization.

The authors indicate that the choice lies between superficial and deep cauterization, and completely ignore conization with the high tension current, and electrocoagulation with the bipolar electrode. It is my practice to disregard the cervix which has been slightly lacerated but is well healed without erosion, ectropion, or infiltration with scar tissue; to cauterize a lacerated cervix with a moderate degree of ectropion or erosion, but which is free from infection; to excise an infected endocervix with the Hyams electrode and the cutting current, or destroy it by electro-coagulation; and to remove a cervix which has been widely lacerated with deep infiltration of the cicatrix, large bulky cysts, associated infection, and ectropion. When there are irregularly eroded or ulcerated areas in the region of the external os, the choice of treatment lies between total hysterectomy and irradiation, rather than between the various types of hysterectomy.

With correct preoperative diagnostic precautions, discriminating treatment of the cervix, and a proper selection of cases, I doubt that the incidence of subsequent carcinoma of the stump is any higher after supravaginal hysterectomy than it is in women who have never been operated upon. In my 654 cases only one instance of carcinoma of the stump has come to my attention, and this was due to a stupid error on my part.

The authors wisely stress the importance of careful preoperative study and preparation of the patient, the value of preoperative transfusions, adequate operative exposure, expeditious technique, and the protection of raw surfaces in the pelvis. When there are denuded areas that cannot be satisfactorily peritonized, I have used sheets of gutta percha tissue for many years to prevent visceral agglutination. This is less cumbersome than rubber tissue. Cashman and Frank are to be congratulated on their low mortality after supravaginal operations, 0.45 per cent, the lowest that has so far come to my attention.

DR. VIRGIL S. COUNSELLER, ROCHESTER, MINN.—On my own service at the clinic approximately 80 per cent of the operations are total hysterectomy and about 20 per cent are subtotal hysterectomy. Little more difficulty is experienced in the removal of the cervix with the fundus from the abdominal side than is encountered in cutting it off and leaving the cervix in position. I have several principal reasons for doing total hysterectomy. One of these is that by so doing the cervix, as a source of infection, is eliminated. Another reason for the total operation is that by means of it the vaginal vault of the multiparous patient can be reconstructed. Dyspareunia will not occur and a much more nearly perfect anatomic reconstruction will be attained.

It has been established that the cardinal ligament is the only useful one in the maintenance of uterine support. Very little can be done with this ligament when subtotal hysterectomy is performed. My plan in removal of the cervix is to shorten the broad ligament and then to re-attach it to the angles of the vagina, and instead of shortening the vagina, I can actually lengthen it.

DR. JOE V. MEIGS, BOSTON, MASS.—In 1932, from one of the hospitals in Boston, came a report of 3,000 cases of cauterization of the cervix with a very small subsequent incidence of cancer. This report was made to show that cauterization would prevent cancer. I accepted that teaching until I had had two patients of my own who developed carcinoma of the stump, both of whom are now dead and could easily have been saved. Since that time I have done total hysterectomies as a practical routine. It is my opinion that it is the operation of choice and is technically as easy to do as a supravaginal operation. I have had only one case of dyspareunia and have asked all of my patients about this symptom.

adipose patient with deep pelvis, and when shortened sacrouterine ligaments and parametrial tissue limit the mobility of the cervix, the technical difficulties are much increased. It is in this group that unnecessary deaths would occur if total hysterectomy were done in every case where hysterectomy is indicated.

CONCLUSIONS

1. Infection plays a prominent part in deaths from hysterectomy.
2. Chronic cervicitis is a source of infection.
3. Deep cauterization of the cervix, as the first stage in hysterectomy, eliminates this source and reduces the mortality.
4. It is advisable in both total and subtotal hysterectomy.
5. It eliminates future inflammatory trouble with the cervical stump and in our experience prevents carcinoma.
6. Deep cauterization of the cervix followed immediately by subtotal hysterectomy has made total hysterectomy unnecessary for benign conditions of the uterus.

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DISCUSSION

DR. WALTER T. DANNREUTHER, NEW YORK, N. Y.—There is little difference in the morbidity and mortality of supravaginal and complete hysterectomy in the hands of experienced operators. I have looked up the records of my last 730 personally performed hysterectomies and found that 654 were supracervical amputations, 65 panhysterectomies, and 11 vaginal hysterectomies. Ten patients died after the supravaginal operations, a mortality of approximately 1.5 per cent. There were no deaths, nor bladder or ureteral injuries, after complete hysterectomy, either abdominal or vaginal, so it is evident that like Cashman and Frank, I am prejudiced in favor of the supravaginal abdominal operation, notwithstanding the zero mortality of the complete operation in my hands. My own reasons for this are because of the marital difficulties and dyspareunia which follow ablation of the cervix. If an inquiry is made of each patient subjected to total hysterectomy, the almost invariable confession of subsequent sexual impairment or unpleasantness becomes a forcible argument in favor of cervical retention. Obviously this premise becomes untenable in the presence of extensive cervical disease or malignant, or potentially malignant, lesions.

Like the authors, I remove the appendix routinely and am convinced that appendectomy introduces no additional risks. I cannot agree with Cashman and Frank that infection constitutes an important hazard in the mortality of hysterectomy, since only one death in my series of cases was due to peritonitis. No one can dispute the fact that a diseased cervical stump predisposes to postoperative morbidity and remains a menace throughout the patient's subsequent life as a

cervix. I doubt if a deep cauterization can be done, whether it is complete or incomplete, without a good deal of stenosis. There are pockets of epithelial growth in the cervix and deep cauterization will not reach and dispose of them.

DR. JAMES W. KENNEDY, PHILADELPHIA, PA.—From the discussions we have just heard, one would be led to think that Dr. Cashman was contrasting the difference in mortality and morbidity of complete removal of the uterus as an abdominal operation, with that of supravaginal amputation of the uterus. The paper is, however, dealing with cauterization of the cervix in order to prevent operative infection from the hysterectomy which was to follow.

I am entirely in accord with the teaching the doctor has advanced. I would as soon undertake to perform a hysterectomy from above or below, without washing my hands, as I would attempt to operate without thoroughly cauterizing the cervix and making a very thorough toilet of the vaginal canal, which is accomplished by soap and scrubbing brush.

Cauterization of the cervix after supravaginal hysterectomy has been performed is a step of great value as a prophylaxis against occurrence of malignancy of the remaining cervix. The teaching is of particular worth to those operators who cannot perform a panhysterectomy with as low mortality as that of supravaginal amputation of the uterus.

Although today the teaching is in favor of a greater number of complete operations, there is a difference in the mortality of a complete hysterectomy as compared with supravaginal amputation of the uterus, in favor of the latter, and especially so in the very fleshy woman with cardiorenal symptoms. There is then a broad field of usefulness for the points brought out in Dr. Cashman's discussion.

Reference has been made to shortening or distortion of the vaginal canal following complete hysterectomy when performed either as a vaginal or abdominal operation by the ligature method. Over 95 per cent of the hysterectomies performed in the Joseph Price Hospital are executed as vaginal hysterectomies by the clamp method, and we find in practically all cases the vaginal canal is lengthened. The only exception to such results occurs in those patients where we have removed an extensive amount of the vaginal fornix for malignancy of the cervix.

DR. MORTIMER N. HYAMS, NEW YORK, N. Y.—Far too frequently when reference is made to chronic endocervicitis, the type or degree is not considered. Based on Mathews' classification, a first-degree involvement would not necessitate the same therapeutic measures as would a fourth. While cauterization of the cervix has advantages in certain forms of cervical pathology, it cannot be considered a cure-all for every form of chronic infection. I believe that the age of the patient and the extent of the pathology in the cervix must be the index for the method of attack.

DR. CASHMAN (closing).—Deep cauterization is our method of treating these cases, but we are in favor of any method that cleans up the cervix in treating cases of cervicitis. A stricture is not a factor when you are doing a hysterectomy.

A recent patient of mine, who had been cauterized twelve years ago, was found to have a cervix honeycombed with cysts, but this was not the result of the kind of cauterization we are talking about. If you are going to deal with the cervix properly you must destroy every bit of epithelium. If cauterization is done completely at the time of operation, no further cauterization is necessary.

We have watched these patients in whom we did not cauterize the normal cervix at the time of hysterectomy, and they have come back with an inflamed cervix later on. In many of these there was no history of leucorrhea. Up to 1938, Dr. Huggins and I did 2,500 subtotal hysterectomies with cauterization of the cervix and with no known carcinoma of the stump in that number. We made a follow-up of 506 of the patients.

DR. A. J. RONGY, NEW YORK, N. Y.—No single surgical procedure is equally applicable in every case. The problem of how to deal with the cervix after a supravaginal hysterectomy has been performed in a multiparous woman, in whom the cervical canal very likely is infected because of old lacerations and scarification, is quite different from the problem the cervix presents in the nulliparous patient, especially the elderly spinster, upon whom a supravaginal hysterectomy has to be performed. When clinically there is no infection of the cervix, especially in the unmarried woman, there is no reason for cauterizing the cervical canal and destroying the glands and its lining. The incidence of cancer of the stump of the cervix is definitely small. The mortality following supravaginal hysterectomy and total hysterectomy in the hands of the expert may not differ much, but in the hands of the average surgeon a supravaginal hysterectomy is much safer for the patient than a total hysterectomy. Surely, the incidence of ureteral injury is practically reduced to a minimum.

In patients with relaxed vaginal vaults, in whom a sagging of the vagina is likely to take place after a supravaginal hysterectomy has been performed, I usually anchor the cervical stump to the anterior parietal peritoneum. That often prevents further sagging of the vaginal vault and occasionally obviates many of the annoyances that take place during sexual intercourse in this group of patients.

DR. WILLIAM H. WEIR, CLEVELAND, OHIO.—In our hospital service, the supravaginal hysterectomies show a higher mortality rate than do the panhysterectomies. The probable explanation of this is that in the more difficult cases, with dense adhesions, abscesses, or other complications, many of the operators, in order to save time, will perform the supravaginal hysterectomy instead of the usual total operation and naturally these complicated cases would show a higher death rate than simpler ones.

We perform a vastly greater number of panhysterectomies than supravaginals and last year we had an unusually lucky series. In a period of thirteen months, 470 consecutive hysterectomies were performed by the visiting and resident staff. No death occurred in this entire series. Of this total, 356 were abdominal panhysterectomies, 65 were supravaginal, and 49 were vaginal.

As far as shortening of the vagina as a result of the panhysterectomy is concerned, it need not occur if one is careful to keep close to the cervix in dividing the vagina and to sacrifice no more vaginal wall than is necessary.

DR. A. D. CAMPBELL, MONTREAL, CANADA.—A cervix that needs to be cauterized should above all others be removed when performing a hysterectomy. Carcinoma in the neglected stump approaches 2 per cent, and it is worthy of note that 80 per cent of these occur where the operation was limited to subtotal hysterectomy for chronic pelvic inflammatory disease. I remove the cervix with the uterus in 70 to 75 per cent of cases, leaving the stump in only the elderly nullipara when removing the uterus for a leiomyoma of the corpus.

In the past seven years following total hysterectomy, our uncorrected death rate including those that died from heart disease, embolism, and progressive malignancy was 1.68 per cent.

DR. CHANNING W. BARRETT, CHICAGO, ILL.—The statistics given in the paper show that these men are in the safe class of operators, but this safety did not come from cauterizing the cervix. If that were true I should have had a great many deaths from peritonitis in subtotal hysterectomies, which I have not had.

There has been too little stress laid upon vaginal hysterectomy. In those cases in which the cervix is badly diseased, either from the standpoint of possible development of carcinoma or a benign condition of the cervix, a vaginal hysterectomy in all cases where it is technically possible is the operation of choice. But if we advocate total hysterectomy from above in all cases, we are going to increase the mortality among the average operators far more than we save from developing carcinoma.

Dr. Miller, of New Orleans, has gone very carefully into the question of stenosis, and he puts deep cauterization as one of the principal causes of stenosis of the

It is of interest to note that in comparing the effects of sodium amytal and pentobarbital, when each is used separately with the same agent, there is a small but notable increase of apnea in the instance of sodium amytal. When used with scopolamine, the increase was found to be 2 per cent; when used with rectal ether, 6 per cent. Fifty per cent of pentobarbital-paraldehyde babies showed apnea, while fully two-thirds of pantopon-scopolamine patients were apneic.

A further study of analgesics and their effects upon the respiration of the newborn infant are furnished in an unpublished report by Dr. Carl P. Huber of our clinic at Indiana University (Table I).

In this series of 656 cases, comparative studies were made of cyclopal and carbromal; cyclopal, carbromal, and rectal ether; sodium pentobarbital; and sodium pentobarbital and rectal ether.

It is noted that the percentages of immediate spontaneous respiration of the various groups are quite comparable, ranging from 65.6 to 77.4 per cent, while the average for the groups was 73.6 per cent. The average "immediate" and "delayed spontaneous" totaled 85 per cent. Twenty-five per cent of the infants were born apneic.

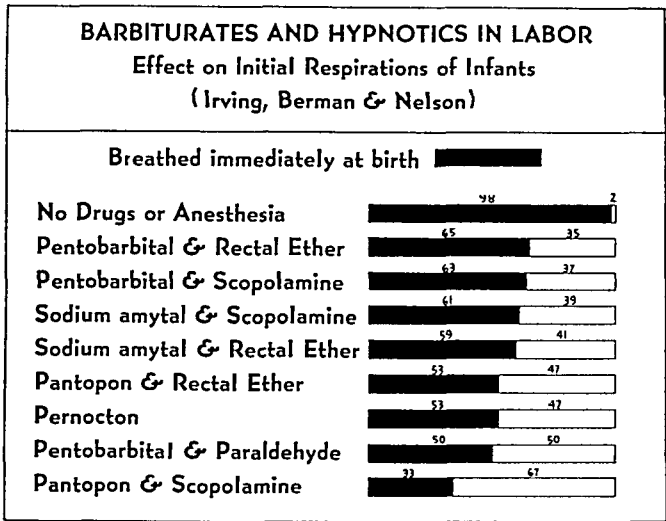


Fig. 1.

TABLE I. THE EFFECT OF CERTAIN ANALGESICS ON INITIAL RESPIRATION OF NEWBORNS
HUBER: OBSTETRICAL DEPARTMENT, INDIANA UNIVERSITY

ANALGESICS	NUMBER OF CASES	SPONTANEOUS AND IMMEDIATE	DELAYED. NO RESUSCITATION	RESUSCITATION	STILLBIRTH RATE
Cyclopal	115	77.4	8.7	11.3	2.6
Cyclopal and rectal ether	96	65.6	17.8	13.5	3.1
Cyclopal and carbromal	87	75.8	12.6	11.5	0.0
Cyclopal, carbromal and rectal ether	111	74.8	9.0	15.3	0.9
Sodium pentobarbital	136	70.6	13.9	12.5	2.9
Sodium pentobarbital and rectal ether	111	77.4	10.8	10.8	0.9
Total	656	Av. 73.6	12.0	12.5	1.8

THE EFFECTS OF ANALGESIA ON THE NEWBORN INFANT*

C. O. McCORMICK, M.D., INDIANAPOLIS, IND.

PERHAPS no single issue divides obstetricians so much as that relating to the use of analgesia. Some do not use it, and criticize it severely; others use it and praise it loudly. Nevertheless, analgesia is indispensable in the modern conduct of labor, and is here to stay.

Among the important reasons against its general acceptance is its purported ill-effect upon the infant. Even strong advocates of childbirth relief share this misgiving to some extent, conceding that in sedating and narcotizing the laboring mother they routinely risk jeopardizing the newborn infant by inducing as a rule at least a brief apnea, and occasionally a marked, sometimes alarming asphyxia.

Certainly, concern in behalf of newborn infants delivered under the influence of maternal analgesia has been strongly bolstered by the report of Schreiber,¹ indicating remote cerebral damage where analgesics are given in excess of pharmacologic doses.

Though long since granted analgesia aids the mother by sparing her mental and physical shock and exhaustion, because of the more or less general presageful feeling mentioned above, there has been but little or no surmise that analgesia might benefit the infant as well as the mother. Gratifyingly enough, recent studies by independent investigators indicate this to be true.

The purpose of this presentation is twofold: First, to show the effects of various analgesic agents in common usage as they reflect upon the initial respiration and mortality of the newborn; and second, to stress the safety of certain popular present-day methods of relief, and compare their enhancements upon the infant. In major part, this will be attempted by correlating the outstanding findings of several investigators.

Regardless of what enhancing effects may result upon the infant, all forms of childbirth relief, except those of local infiltration, do have a large and variable incidence of at least one ill-effect, namely, depression of the respiratory center. This was well illustrated by the study of Irving and his co-workers,² covering eight types of analgesia (Fig. 1).

In the most favorable instance apnea occurred in 35 per cent of the cases. This is in marked contrast to the 2 per cent incidence found among cases without relief medication. In the extreme instance, the percentage of apnea rises to 67 per cent.

It is observed that pentobarbital and rectal ether, the modified Gwathmey method, holds the most favorable position. The pentobarbital-scopolamine method, probably the one most generally used today, holds a close second position.

*Read at the Fifty-Third Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Excelsior Springs, Mo., September 26 to 28, 1940.

inhalation lasted from fifteen to sixty minutes, the weight loss was 5 per cent; and where ether was employed over one hour, the loss was only 4 per cent of the birth weight.

Also, babies born to etherized mothers regained their birth weight more rapidly than those born to mothers receiving no anesthesia. Where the mothers had no medication, the average baby's weight was still 2.37 per cent below birth weight on the eighth day; while the average weight of those babies born to mothers having ether over one hour exceeded the birth weight 0.58 per cent on the eighth day.

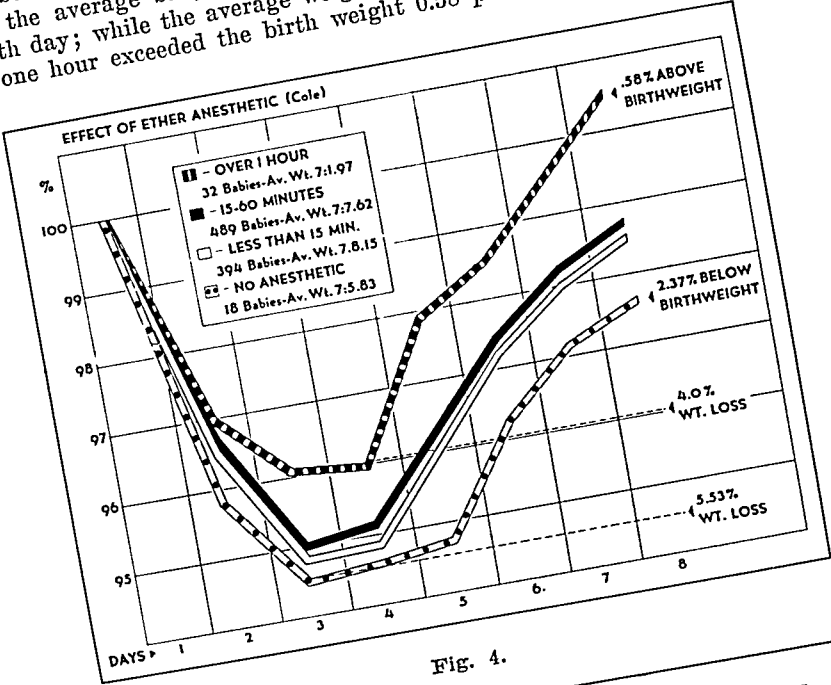


Fig. 4.

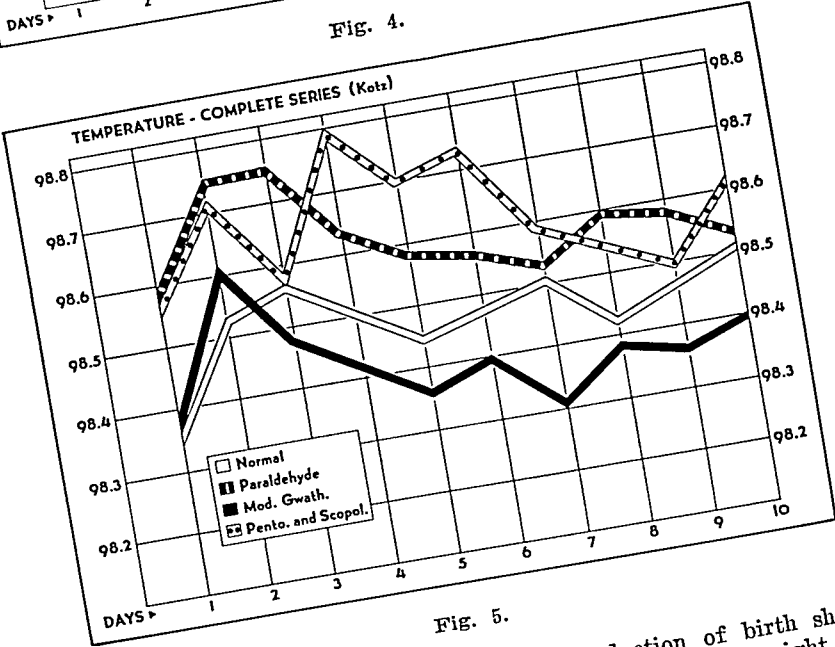


Fig. 5.

Cole attributes this favorable showing to the reduction of birth shock in the baby, and rightfully points out that the so-called "physiologic weight loss" may be more than just physiologic, and perhaps is a direct index of the amount of shock.

Early neonatal welfare is indicated by at least three factors: the daily temperature curve, the amount of weight loss, and the rate of weight loss recovery.

Kotz and Kan well proved the analgesic effect of the control series were handled. The influence of 100 under parative anal effect upon the babies. It is not had Gwath the latter diverges. It is may method.

Fortunately apnea appears to have no serious ill-effect upon the life of newborn infants. Presumably this is partially due to the normal anoxemic state before birth. The gross stillbirth rate of Irving's group was 0.93 per cent, that of Huber's, 1.83 per cent.

Any bona fide effect of an analgesic agent should reflect in the stillbirth and neonatal mortality rates. Clifford and Irving,³ by checking into the stillbirth and neonatal losses at the Boston Lying-in Hospital over a five-year period, preceding the use of barbiturates and a like period following the introduction of barbiturate analgesia, discovered that both the stillbirth and neonatal mortality rates decreased during the barbiturate period (Fig. 2).

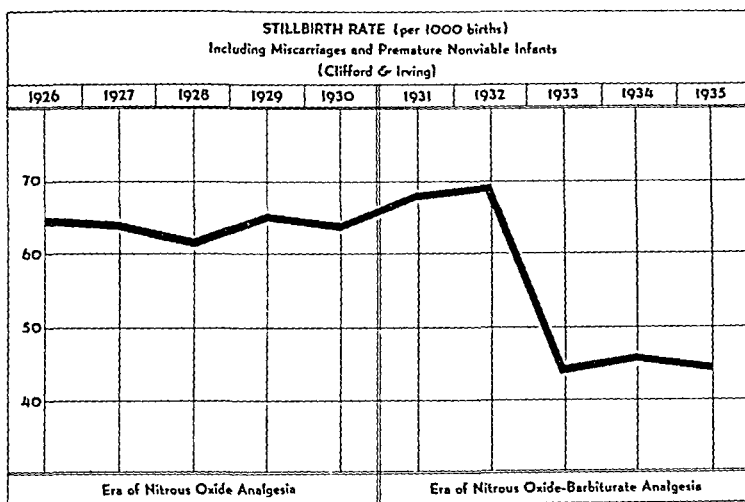


Fig. 2.

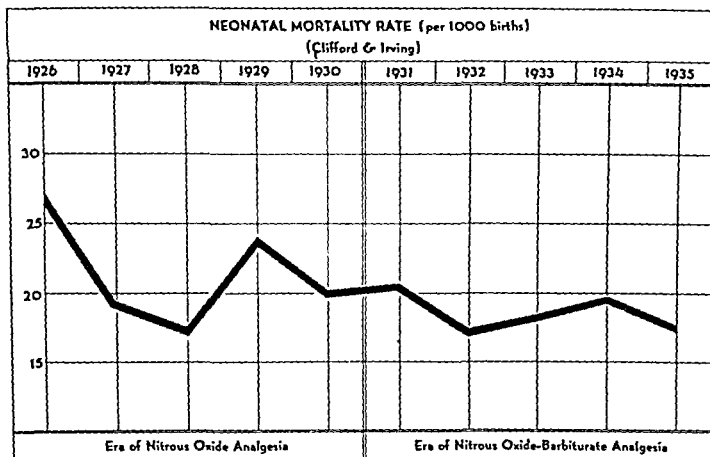


Fig. 3.

The stillbirth rate fell from 65 per 1,000 births during the prebarbiturate era to 46 in the following five years, and the neonatal loss dropped from 27 to 18 per 1,000 births (Fig. 3).

Among the first studies to show benefit from maternal analgesia or anesthesia to the newborn infant was that of Cole,⁴ in which he analyzed the effect of ether anesthesia (Fig. 4).

Babies born to unanesthetized mothers experienced a maximum loss of 5.53 per cent of the birth weight. Those born to mothers, who had less than fifteen minutes of inhalation ether, had a maximum loss of 5.2 per cent. Where the ether

It is noted that the results of the paraldehyde and modified Gwathmey methods show more favorably than those of the normal and pentobarbital-scopolamine groups throughout the first six days. Also, the greatest maximum weight loss occurs among babies born to mothers having no analgesia and to those having pentobarbital-scopolamine. It is further observed that babies born under the influence of the modified Gwathmey method return to normal weight more rapidly than those delivered under either paraldehyde or pentobarbital-scopolamine.

In comparing the maximum weight loss of each of the three forms of relief and that of the normal group (Table III), it is observed that the greatest loss occurs among babies born to mothers having no medication.

TABLE III. AVERAGE TOTAL WEIGHT LOSS ON THIRD DAY (KOTZ)

	OZ.
Control (100 babies)	4.7
Pentobarbital and scopolamine (99 babies)	4.6
Paraldehyde (498 babies)	4.5
Modified Gwathmey (98 babies)	4.1

Those born under either the pentobarbital-scopolamine or paraldehyde methods suffer an average total weight loss almost equal to that of the normal group, while the babies born under the modified Gwathmey method are favored by a definitely less weight loss. The average of the first three groups is 4.6 ounces, that of the latter, 4.1 ounces.

Another study affords a comparison of the results of various types of deliveries as performed upon mothers having no analgesia and those having one of the three forms, paraldehyde, modified Gwathmey, and pentobarbital-scopolamine (Table IV). This study is important because that which alters the type of delivery may reflect upon the welfare of the infant.

TABLE IV. TYPES OF DELIVERY (KOTZ)

	NORMAL %	PARALDEHYDE %	MODIFIED GWATHMEY %	PENTOBARBITAL AND SCOPOLAMINE %
Low Forcep	2	81.4	21	87.5
Midforcep	1	10.3	3	4.0
Breech	3	3.3	5	8.0
Version Extraction	0	0.5	1	0
Spontaneous	94	4.5	70	4.0

The low percentage of patients delivered by low forceps in the normal group is quite striking compared with the high rate in either of the analgesia groups. However, the low incidence of employment of low forceps among the modified

TABLE V. EFFECT OF SEDATIVES AND ANESTHESIA ON THE MORTALITY OF PREMATURE INFANTS

2,500 GRAMS OR LESS (GRIER)

	TOTAL CASES	CASES LIVED	CASES DIED	MORTALITY %
No sedative or anesthesia	18	10	8	44
Local infiltration	21	17	4	19
Sedative only	19	14	5	26
Anesthetic only	236	172	64	27
Sedative and anesthesia	155	125	30	19
Not stated	4	2	2	50
Total	453	340	113	25
				Av. Gr.

Kotz and Kaufman⁵ in their outstanding work, based upon these three standards, have well proved from the viewpoint of the infant's welfare the justification of wisely used analgesia. His study, covering 700 analgized delivery cases, was directed upon the analgesic effect on the infant. The temperature, weight loss, and weight gain during the first ten days of life were closely followed. In addition he ran a control series of 100 babies born to mothers receiving no medication. *All babies were handled under similar nursing care.*

The group of 700 analgized mothers consisted of 500 delivered under the influence of paraldehyde, 100 under pentobarbital-scopolamine, and the remaining 100 under the modified Gwathmey method. His work further included a comparative analysis of these three commonly used forms of relief as to their respective effect upon the infant.

The observed temperatures in each of the three methods studied and that of the babies born to unmedicated mothers are shown in Fig. 5.

It is noted that the temperature of the paraldehyde group and that of the modified Gwathmey method run quite parallel to normal, the former slightly above and the latter slightly below. In contrast, that of the pentobarbital-scopolamine series diverges, running higher, especially on the third, fourth, and fifth days.

It is to be observed in Table II that both the paraldehyde and modified Gwathmey methods present a more favorable showing than the normal, and of the two methods, the paraldehyde is the slightly more favorable.

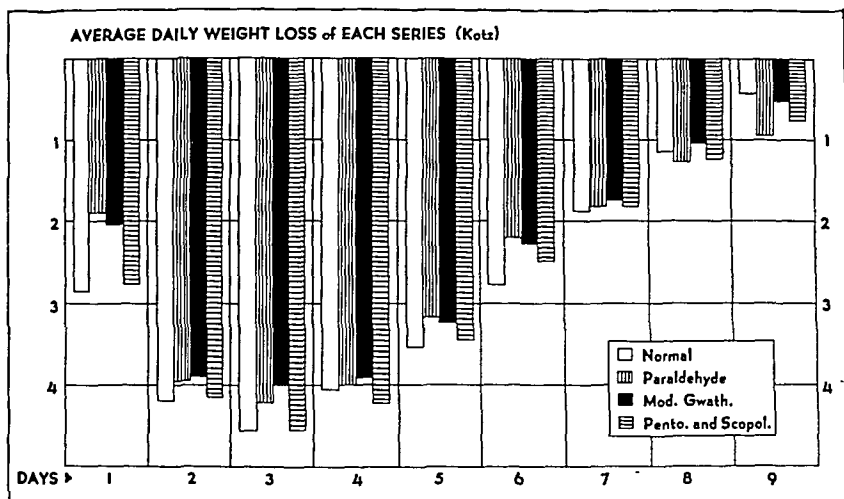


Fig. 6.

TABLE II. PERCENTAGE OF BABIES WITH TEMPERATURES OVER 100° F. (KOTZ)

	DAY POST PARTUM									
	1ST	2ND	3RD	4TH	5TH	6TH	7TH	8TH	9TH	10TH
Normal	2	4	4	5.	2	2	1	0	1	0
Paraldehyde	1.4	2.2	3.6	1.6	1.8	1.4	1	0.4	0.2	0.4
Modified Gwathmey	1	4	2	4	1	1	1	1	1	1
Pentobarbital and scopolamine	1	8.3	4.1	8.3	8.3	8.3	2	4.1	4.1	1

Here again, the pentobarbital-scopolamine method stands out in unfavorable contrast. On the second, fourth, fifth, and sixth days, 8.3 per cent of the patients ran a temperature of over 100° F., from two to eight times that of either of the other two analgesic groups.

Further studies compare the average daily weight loss of each of the methods of relief and that of the normal group (Fig. 6).

Clifford's study further reveals that the mortality rate of prematures born to mothers receiving morphine varies in direct relation to the amount of the drug given (Fig. 8).

These findings strongly substantiate the long commonly held opinion that opium derivatives, when administered within a few hours of birth, render a deleterious effect upon the infant.

Owing to the popular use of nitrous oxide-oxygen in maternal analgesia and anesthesia, special reference should be made to its action upon the newborn.

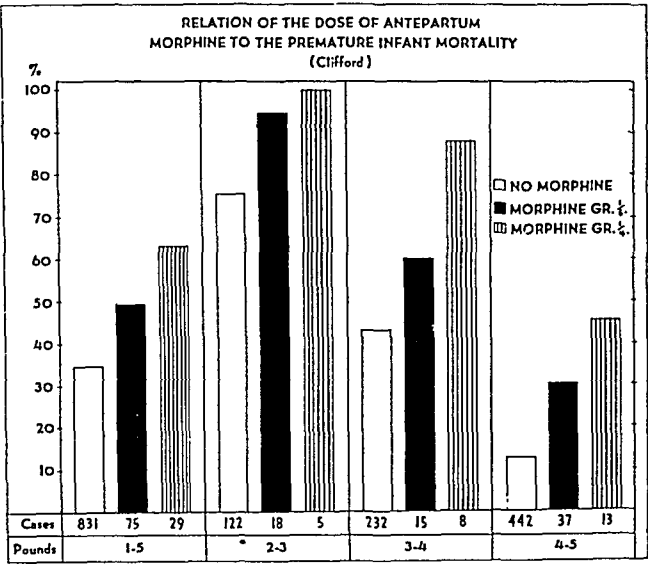


Fig. 8.

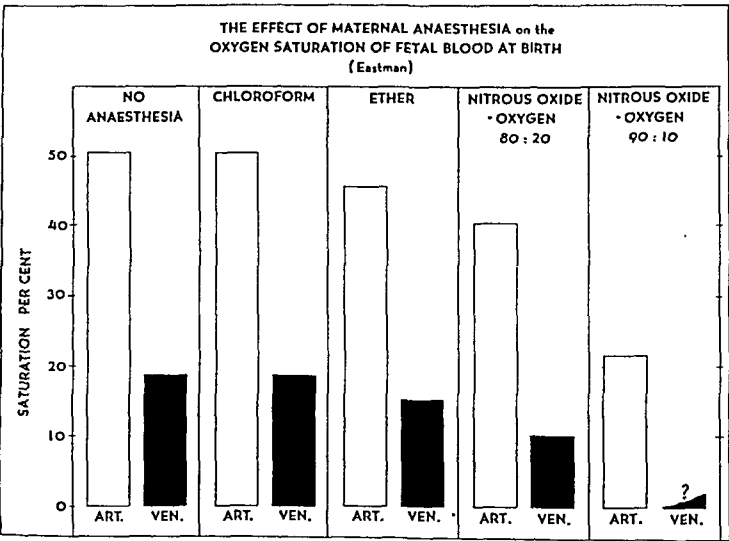


Fig. 9.

Eastmans has demonstrated its production of fetal anoxemia (Fig. 9), and points out the risk of profound asphyxia when concentrations higher than 85:15 are employed. His study showed that when concentrations of 90:10 or stronger were used over a period exceeding five minutes one-third of the babies suffer a marked anoxemia, and occasionally profound asphyxia results.

Gwathmey group compares very favorably with the much higher rates found in the paraldehyde and pentobarbital-scopolamine series. Also, the 70 per cent incidence of spontaneous deliveries in the modified Gwathmey series is noteworthy when contrasted with the 4.5 per cent and the 4 per cent incidence noted, respectively, among the paraldehyde and pentobarbital-scopolamine groups.

In summarizing briefly this study of Kotz, it is indicated, at least, that the two forms of obstetric analgesia, paraldehyde and modified Gwathmey methods, are favorable to the infant. Further, that of these two, the modified Gwathmey appears to be the more favorable. Regarding the pentobarbital-scopolamine method, the data presented would indicate that its effect upon the baby is adverse.

A discussion such as this properly includes special reference to the effect of sedation and anesthesia upon the life of premature infants. In this instance interest is prompted not solely in behalf of life-saving, but to take advantage of their susceptibility to reaction.

One such study has been made by Grier and Lussky⁶ who analyzed the mortality effects of sedatives and anesthesia in a survey of 453 premature infants, weighing 2,500 Gm. or less (Table V).

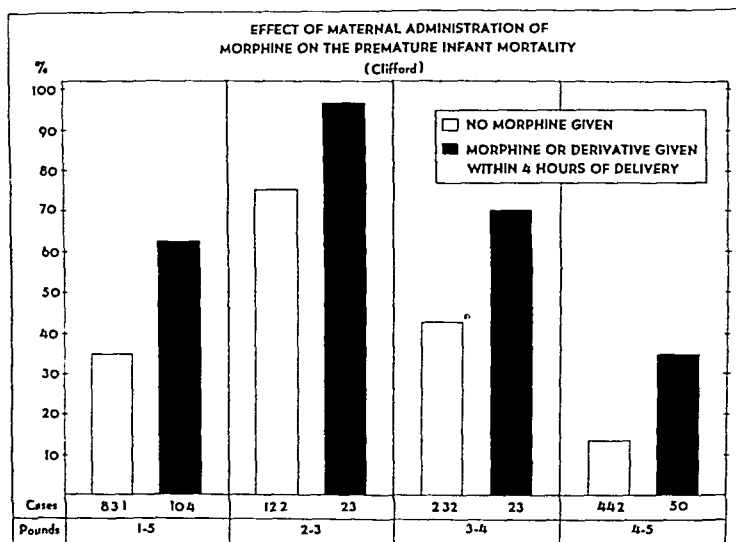


Fig. 7.

Certain observations are noteworthy. For example, the mortality rate among those delivered under both sedation and anesthesia, numbering 155 or a full third of the group, was only 19 per cent. This rate was the same as that for infants whose mothers had only local infiltration, and was less than the average gross mortality rate of 25 per cent. Also, the rates of the two groups, "sedatives only" and "anesthesia only" were, respectively, 26 and 27 per cent, closely approximating the gross mortality rate. The small number of 18 patients, in whom no medication was administered, presented a rate of 44 per cent, the highest of all.

Admittedly this study is not one of close analysis, and no doubt were some of its data broken down deductions might not be so favorable. Yet the statement remains, that the mortality rate among 155 premature infants weighing 2,500 Gm. or less born to sedated and anesthetized mothers was only 19 per cent.

A more pertinent investigation, particularly as relates to the use of opiates, is that of Clifford,⁷ which shows the striking effect upon premature infant life of morphine and its derivatives when administered within four hours of birth (Fig. 7).

The mortality rate of infants having received morphine was twice that of those born to mothers not receiving the drug.

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DISCUSSION

DR. EMMETT D. COLVIN, ATLANTA, GA.—Schreiber has confronted the obstetricians with an important problem, for he has clearly shown that a relationship between asphyxia at birth and serious degenerative brain changes exists. He concludes that drugs, administered for the relief of maternal pain during labor, may be the causative factor.

He has pointed out a danger which obstetricians thought did not exist. At least the general feeling has been that babies with simple apnea, once resuscitated were safe and developed along a normal course. Of course, Schreiber did not attempt to determine the exact role played by dystocia, operative interference, oxytocics, and general anesthesia. It is therefore, unfair to condemn amnesia and analgesia methods without evaluating these factors.

In discussing this subject, one must constantly keep in mind the influence of drugs upon the increased incidence of uterine inertia and operative termination of labor. Analgesic drugs, by creating the necessity for operative delivery and the accompanying increased incidence of intracranial injury, are responsible indirectly for the asphyxia so frequently encountered among injured babies.

Since 1932, Bartholomew and I have employed 3 gr. of nembutal (pentobarbital sodium) and 6 drams of paraldehyde, by mouth, in the conduct of 2,363 private cases. When necessary, supplementary small doses of paraldehyde were used as indicated in order to secure sleep. In an occasional case a small dose of morphine and scopolamine preceded the initial dose of paraldehyde. The effect of the drug itself upon the mother or child has not caused apprehension, on the part of the attendants, in a single case among the 2,363 deliveries.

An analysis of our series yielded the following data: complete amnesia in 92 per cent; partial amnesia in 6 per cent and failure in 2 per cent; troublesome restlessness in 7 per cent; spontaneous delivery in 80 per cent; average duration of labor in nulliparas, thirteen hours and eighteen minutes; in multiparas eight hours and fifty minutes; and a corrected fetal mortality of 1 per cent.

The incidence of apnea among term babies was 9 per cent. This apnea seemed to be due to a state of drowsiness rather than to a respiratory depression. We have not noted a detrimental neonatal effect. Clearing of the air passages, followed by spanking or gentle mouth-to-mouth inflation of the lungs promptly established good respiration and crying. The apnea was prolonged if morphine and scopolamine preceded the paraldehyde. We found that with premature infants the apnea was exaggerated, and sluggishness predisposed to atelectasis. Aside from drowsiness, in the first six to eight hours after birth, term babies showed no difference in nursing, temperature curve, gain in weight, and behavior from babies delivered without the aid of paraldehyde.

We believe that paraldehyde in combination with a small dose of pentobarbital sodium is a safe method to be employed in childbirth, and, in the hands of capable obstetricians, should not result in greater danger to the mother or infant than drop ether.

DR. W. WAYNE BABCOCK, PHILADELPHIA, PA.—Dr. McCormick's paper brings attention to the very important question: What percentage of "stillbirths" and of deaths in early infancy result from narcotics and anesthetics given to the mother during labor? I question if this danger ever has been overestimated.

Anesthetics and narcotics commonly produce anoxemia, which our expert neuropathologists have shown may greatly damage the brain. Even cyclopropane, pre-

From the viewpoint of anoxemia produced, cyclopropane with the customarily high percentage of oxygen is a more practical analgesic agent than nitrous oxide-oxygen.

More substantial information relative to the influence of maternal analgesia upon the life of the newborn may be gained by comparing the average stillbirth rate of several series of infants born to analgized mothers with that of the stillbirth rate in general. The compilation at hand (Table VI), presents the average rate of the former group to be 1.87 per cent, while that of the general group is conservatively stated by most authors to be in excess of 4 per cent.

TABLE VI. STILLBIRTH RATES OF INFANTS BORN TO ANALGIZED MOTHERS

SERIES	NUMBER OF MOTHERS	NUMBER OF STILLBIRTHS (GROSS)	STILLBIRTH RATE % UNCORRECTED
Galloway et al. ⁹	1,415	31	2.19
Huber ¹⁰	656	12	1.83
Irving et al. ²	860	7	0.93
Kotz and Kaufman ⁵	700	14	2.00
Krebs et al. ¹¹	3,720	60	1.61
Lewis ¹²	500	15	3.00
McCormick ¹³	1,929	45	2.33*
Whitefield ¹⁴	744	13	1.76
Total	10,524	197	1.87
			Av. Gross

*Includes premature nonviable infants, antenatal deaths, and stillbirths of all operative cases.

This favorable showing by no means should be fully accredited to the use of analgesia, since as a whole patients who receive analgesia also receive better obstetric care, both during the prenatal period and at the time of delivery. On the other hand from the data presented, it is seemingly true that many varieties of popular analgesia do not react adversely upon the life of the newborn infant.

CONCLUSIONS

1. The high degree of general safety and security for the newborn as revealed by a correlated study of the many modern varieties of child-birth relief is reassuring.

2. Opiates are probably the only analgesics that may materially affect the infant adversely, and may be particularly hazardous in cases of prematurity.

3. Based upon augmenting the welfare of the newborn, the three standard analgesic methods, modified Gwathmey, paraldehyde, and pentobarbital-scopolamine, appear to rate in the order named.

4. By eliminating the "physiologic weight loss" (birth shock) and enhancing the fetal and neonatal welfare, wisely used obstetric analgesia is no longer a privilege but a prerequisite of better obstetrics.

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percentage of these babies that we cannot determine the cause of death. There are thus other than the morphologic factors concerned in the death of these babies who die before or soon after they are born.

So far as Dr. Schreiber's experimental work is concerned, it tallies with our clinical observations that the barbiturates are very depressing. I would also emphasize that the effect of these drugs is apparently not a direct effect on the fetus so much as on the mechanism of labor and the establishment of respiration in the newborn. That and the anoxemia that accompanies it are the real factors. Consequently not only the depth but the duration of the anoxemia is extremely important, and we should realize the great importance of promptly securing oxygen for the newborn baby.

In the statistics on weight loss there was no base established to show the original weight of the infants. We all know that the heavier infant will lose more weight in actual ounces than the smaller infant. In these tables there was nothing that showed what the weight was at birth, nor any comparison between the different groups as to their actual weight.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—I was in the clinic of a very well-known European obstetrician some years ago and brought up this subject of labor analgesia. He said that since so many articles had appeared in popular American magazines, all of his patients demanded that they be given pain relief, and that he had devised something which was very effectual. He gave them a small two-ounce bottle and told them to take half the contents when the pain began and, in another hour or two to take the other half. When they awakened they asked for more. He said it was merely brandy, and they were half "tight" when they were delivered, and consequently remembered little of what had taken place. In his opinion the procedure was effective and harmless and did not hurt the baby.

DR. McCORMICK (closing).—Dr. Babcock properly directs attention to a broader view of our subject by inquiring as to neonatal deaths following the use of analgesia. Of the various current reports studied, only one afforded this information. Krebs and his co-workers in a series of 3,720 cases recorded 36 infant deaths, while the mothers remained in the hospital, an incidence of 0.97 per cent. In a series of 3,446 infants born to unanalgesized mothers, they found 48 such infant deaths, or an incidence of 1.39 per cent.

I might add that in four major maternities in Indianapolis where analgesia, for the most part the modified Gwathmey method, has been used for the past ten years in an excess of 30,000 cases, vital statistics do not reveal an increase in either stillbirths or neonatal deaths.

Schreiber's work was based upon unpharmacologic dosage of certain analgesics, and although a most important and invaluable study, it does not properly apply to intelligently used analgesia, such as implied in our presentation.

I wonder if it is Dr. Adair's impression that there is a greater incidence of unexplained stillbirths and neonatal deaths since the advent of modern analgesia. No doubt the massive doses of barbiturates, such as 9 to more than 20 gr. of pentobarbital as employed by some, may produce undesirable anoxemia by both interfering with mechanism of labor and by hindering the establishment of respiration. We avoid this danger in our clinic by using small divided doses, $1\frac{1}{2}$ to $4\frac{1}{2}$ gr., in conjunction with rectal ether, a patient rarely receiving more than a total of $7\frac{1}{2}$ gr.

Dr. Adair's assertion that the statistics presented relative to weight loss were misconstrued seems not to be fully correct. In the first place, granted the larger the baby the greater the weight loss and the smaller the baby the less the weight loss, the importance of such a variation diminishes as the size of the series increases. In that the series cited were reasonably large, and the infants were given similar nursery care, it would appear that any effect registering consistently would be practically significant. In the instance of Fig. 4, such an error was offset by expressing the weight loss in percentage of birth weight.

scribed for the high percentage of oxygen with which it may be used, has caused permanent cerebral damage or death. I know of several deaths occurring at the Philadelphia General Hospital several days after operation from this cause. These deaths had been attributed to other conditions until the histopathology of the brain was revealed.

The anoxemia incident to the administration of general anesthetics and narcotics has in my experience been the most important single factor in the mortality following operations upon young babies. As a result we use only local anesthetics for the newborn infants.

Ravdin and his group have shown that even the serious degenerative change occurring in the liver under chloroform anesthesia may be prevented by the associated use of oxygen. The difficulty in preventing some degree of cyanosis renders nitrous oxide-oxygen and even ethylene anesthetics dangerous for prolonged administration. Doubtless careful postoperative studies would show more frequent cerebral damage from anoxemia in the living than is generally recognized. Oxygen should not be withheld if there is any degree of prolonged anoxemia in either infant or adult.

DR. WARD F. SEELEY, DETROIT, MICH.—In Detroit where the work of Schreiber and Cole was done we have been very sensitive to the question of anoxia. We are not so much concerned with a high primary fetal mortality after the use of analgesia, for needless to say if this occurred we would discontinue its use. We are concerned, however, with the "devastation areas" in the brain which manifest themselves much later and can be demonstrated at autopsy by a competent neuropathologist.

The burden of proof would seem to be with us. We have to show that we do not get babies with such devastated brain areas with properly controlled analgesia. This is difficult because in many instances the results of anoxia do not manifest themselves at once, and it is only when the child comes under the care of the pediatrician or neurosurgeon, with mental defect, that the true state of affairs is recognized.

DR. G. D. ROYSTON, ST. LOUIS, MO.—There are two points in this presentation I should like to emphasize: First, apnea is often associated with delay of the fetal head at the vulval ring, regardless of the employment of analgesia. Second, opium in any form is a respiratory depressant. Laboratory studies in the Washington University Clinic have shown that it depresses the respiratory system and constricts the bronchioles. These studies, together with a clinical experience of more than 20,000 deliveries, also show that hyoscine or scopolamine in moderate dosage exerts no effect upon either heart or respiration of the newborn.

Fetal damage seems to depend upon the depth and extent of the anoxemia, whether caused by injections or the inhalations.

In the chart shown by Dr. McCormick it is interesting to note that 3,720 cases reported by my associate, Dr. Krebs, showed an uncorrected fetal mortality of 1.61 per cent. Krebs reported the largest number of cases and his fetal mortality was the lowest in this chart, being outranked only by Irving who reported a smaller number of cases.

There are many variations of analgesic administration. My personal custom is to wait until satisfied that labor is definitely in progress, then to give by mouth 3 gr. of nembutal and 1 c.c. of hyoscine hydrobromide intramuscularly. The nembutal is never repeated, but forty-five minutes after the first dose a second injection of 1 c.c. of hyoscine is given, followed forty-five minutes later by a third injection of 0.5 c.c. After this third dose 0.5 c.c. of hyoscine is injected every one and one-half to two hours until the patient is delivered. This analgesia for more than twenty-five years has been safe in our hands, and what test is better than a clinical experience of more than 20,000 cases? It enables us to limit certain major obstetric procedures to none or to those of minor import.

DR. FRED L. ADAIR, CHICAGO, ILL.—We have been very much interested in the problem of determining the causes of stillbirths and neonatal deaths, and as far as the autopsies are concerned, I would point out that we find in a considerable

enema is given the day before the operation; and the morning of the operation a high cleansing enema is given.

The technique of the vaginal flap operation and restoration of the pelvic supportive structures are shown in illustrations taken at operation and reproduced by an artist.

Fig. 1 shows the laceration in situ, and configuration of the pelvic structures. In addition, the retracting of the posterior vaginal wall is illustrated with the outlining of the vaginal flap which begins outside the dimples formed by the retracted sphincter and continues as outlined. Finally, the flap is shown dissected in close

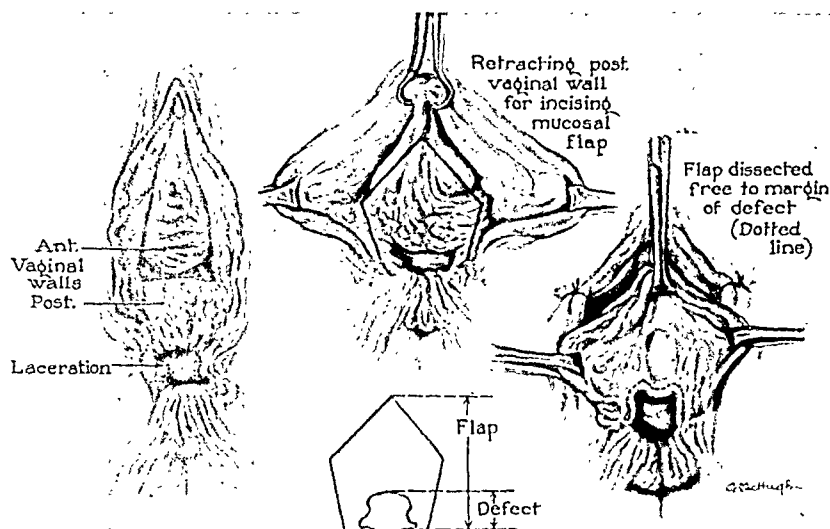


Fig. 1.

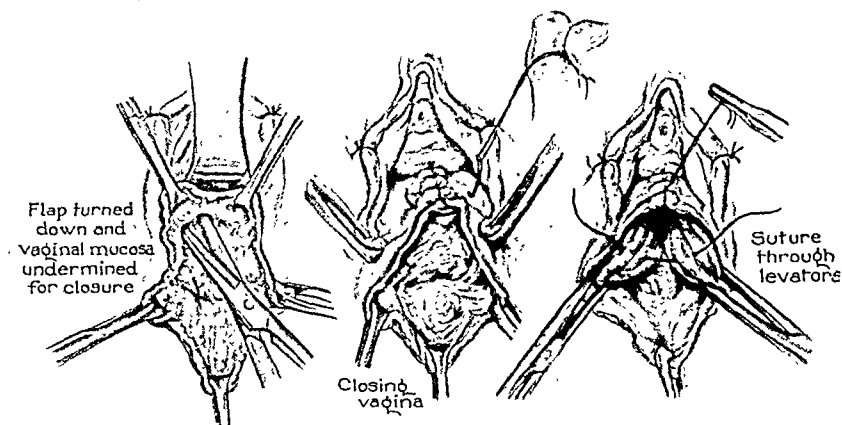


Fig. 2.

proximity to the free margin of the laceration, as illustrated by the dotted line, and is pulled upward by three Allis forceps. A diagram of the relation of the flap to the defect is shown.

Fig. 2 shows the vaginal flap turned down, closing the defect in the anterior rectal wall. The vaginal wall is being undermined by scissors to facilitate the closure. The closure of the vaginal mucosa, the restoration of the urogenital diaphragm, and the obliteration of the dead space is being accomplished by interrupted sutures of No. 1 chromic gut. The levators are being brought together by No. 2 chromic gut.

A REPORT ON A SERIES OF COMPLETE TEARS OF THE PERINEUM WITH EXTENSION UP THE POSTERIOR VAGINAL WALL, REPAIRED BY THE VAGINAL FLAP METHOD*

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THE vaginal flap operation for chronic complete tears of the sphincter of the anus with extension into the rectum and up the posterior vaginal wall is not a new procedure. As early as 1882 Warren described the vaginal flap operation in his monumental presentation. Two years later Ristine added an important publication. Since these early contributions several writers have published articles upon this subject, notably Phaneuf,⁵ Miller,³ Farrar,² and others. To those interested in a most complete bibliography and historical background upon this subject, a reference may be made to the important article of Norman F. Miller entitled "The Surgical Treatment of Complete Perineal Tears."³

It is the essayist's conviction that too few physicians are familiar with the vaginal flap technique and its excellent results, and he does not exclude obstetricians and gynecologists. In addition, most of my patients have come from the general practitioners of medicine who are the larger group practicing obstetrics in this country.

I am reporting a series of 39 patients upon whom I have operated and have been responsible for their complete supervision. The operation to be described in this series differs from the original Warren technique as noted in the vaginal flap dissection, and the repairing of the triangular ligament and the pelvic floor.

In general, it is true that most operators differ slightly in the detailed technique of the vaginal flap operation and the restoration of the supportive structures; however, they are fundamentally accomplishing the same results as to reparation and successful functioning end results. Miller has so aptly pointed out that the success of any plastic operation is dependent upon a good blood supply, absence of infection, and the avoidance of suture tension. Phaneuf gives warning and stresses not only a meticulous technique but emphasizes the necessity of a careful preoperative and postoperative treatment under the immediate supervision of the operator.

TECHNIQUE

It is important to do a reparative operation several months after confinement when involution is complete and at a time immediately following the menses.

The preoperative preparation of a patient is most important. A low residue diet should be given three to four days preceding the operation. An ounce of castor oil is given daily three to four days prior to the operation. A soapsuds

*Read at the Fifty-Third Annual Meeting of the American Association of Obstetricians and Gynecologists, Excelsior Springs, Missouri, September 26 to 28, 1940.

The postoperative care is equally as important as the preoperative care. The knees are tied together immediately following the operation and kept in that position until the cooperation of the patient is dependable.

One of the opiates, or a combination of lead and opium, is given daily over a ten-day period to keep the patient constipated. On the evening of the ninth day a rectal instillation of warm oil is given and retained. If the patient develops an urge to empty the bowel before the next morning, a low soapsuds enema, small in amount, is immediately given. However, if the patient goes until morning without evacuation, a soapsuds enema is given at that time. In conjunction with the rectal instillations mineral oil or saline cathartics may be administered orally.

During the first few days a retention catheter may be placed in the bladder to prevent soiling of the perineum by urine. A potassium permanganate solution has been used to cleanse the perineum when soiling occurs.

It has been our practice to give no local treatment to the perineum except Zoalite, which has been used in some instances to make the patients more comfortable.

The age of the patients varied from 25 to 64 years, with no small number between 45 and 60 years. The average age was 35 years. The average parity was four. The average duration of the tears in this series was fifteen years. Seventy-six per cent of the tears in the series occurred in primiparas. Eighty-two per cent of the series had forceps operations. Function was restored in the control of the

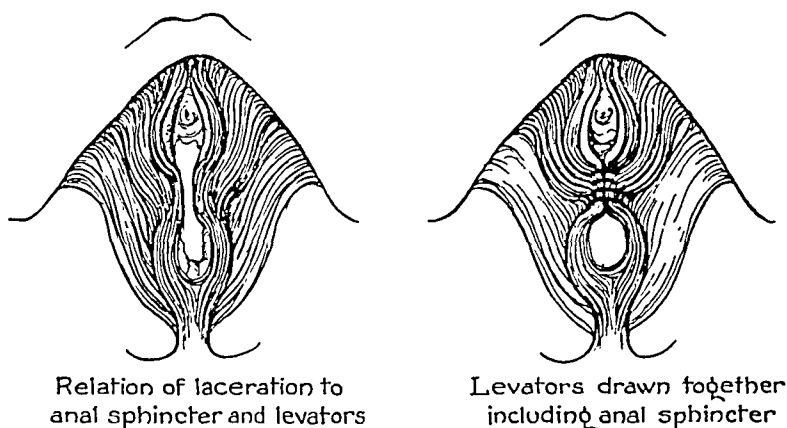


Fig. 5.

fecal stream in 37 of the 39 cases, or 95 per cent. Two cases, or 5 per cent, ended in failure; one developed a rectovaginal fistula with poor control, and the other sloughed the vaginal flap with a complete breakdown of the rectal sphincter. Both of these cases were infected and showed typical temperature elevations; while in the remainder of the series the temperature curves were flat, with the exception of one case which received a good functional result.

It was observed that in only two of the cases had there been a previous attempt at repair. This was a most unexpected finding.

It is interesting to note that in reviewing the records for this series, but not counted in the series, there were five cases of rectovaginal fistulas in which there was incision and conversion comparable to a complete laceration. These cases were repaired by the vaginal flap method and obtained excellent results.

SUMMARY AND COMMENT

1. This series includes 39 cases of chronic complete laceration of the perineum with vaginal wall extension, in which the vaginal flap operation showed a successful result in 95 per cent of the cases. These results compare favorably with those of Miller, Farrar, Phaneuf, and others.

2. Seventy-six per cent of the patients were primiparas.

Fig. 3 illustrates the continued approximation of the levator muscles over the vaginal flap by interrupted sutures of No. 2 chromic gut, and the deep sutures of No. 1 chromic gut approximating the torn ends of the sphincter.

Fig. 4 shows complete closure of the vagina and deep interrupted sutures of No. 1 chromic gut inserted through the constrictor cunei; likewise the levators and the rectal sphincter have been sutured together. Colles' fascia is being closed with interrupted sutures of No. 1 chromic gut. The skin is closed with interrupted sutures of No. 1 chromic gut. The skin is closed with interrupted sutures of No. 1 chromic gut.

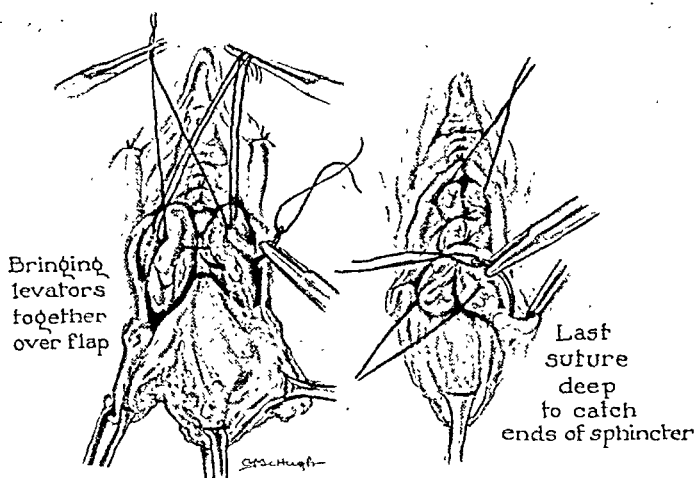


Fig. 3.

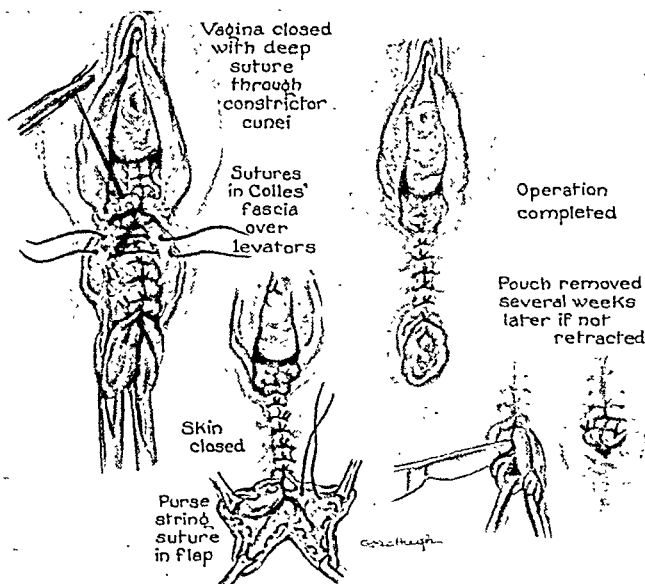


Fig. 4.

sutures of No. 1 chromic gut. The vaginal flap is opened, four Allis forceps are inserted and a purse-string suture is placed in the flap. Finally, the flap is shown after inversion by the purse string. A pouch is being removed several weeks after operation when it fails to retract or shrink down; the final result after removal of the flap is shown.

Fig. 5 is a diagram which shows the relation of the laceration to the anal sphincter and levators, and the relation of the sphincter and levators to each other. The last sketch shows the levators and sphincter drawn together by interrupted sutures.

This operation was recently performed on a young woman with a rectovaginal fistula adjacent but external to the hymenal ring. The anus was dilated and a semicircular incision of the anterior half of the rectum made at the mucocutaneous junction. With a finger in the rectum (Fig. 2) the rectal mucous membrane and muscularis were grasped and carefully dissected until sufficient mobilization without tension had been secured to bring the intact rectum above the fistulous opening to the anal ring. Excess rectum was cut away, and the intact end sutured to the skin of the anus (Fig. 3). Gloves were changed, and the fistulous tract attacked (Fig. 4) and extirpated from the vaginal side.



Fig. 1.

When carried out on a patient with a complete tear with extension up the posterior vaginal wall, an incision is made through the edge of the vaginal mucous membrane at its junction with the rectum. The posterior vaginal wall is dissected from the anterior rectal wall with the greatest of care, since a hole inadvertently made into the rectum will jeopardize the entire success of the operation. Once begun, there is generally little scar tissue to complicate or prejudice this dissection, which is carried halfway to the cervix. The remainder of the operation including the repair of the sphincter is similar to the procedure outlined by Dr. Campbell. Using such technique, 8 patients with tears, involving the anal sphincter and 1 to 4 cm. of the posterior vaginal wall, and two patients with rectovaginal fistulas re-

3. Eighty-two per cent of the patients received a laceration in conjunction with a forceps operation, a most important observation.
4. The average duration of the tear was fifteen years.
5. A previous attempt at repair was noted in only two cases.
6. The technique of the operative procedure taken directly at the time of operation has been reproduced by an artist.
7. All cases were repaired by catgut except five, in which silver wire was used in part. This shows that excellent results can be obtained by catgut alone; and it is my impression that the finer gauge gut is as useful as the heavier. In no instance were continuous sutures used.
8. Infection was a serious factor in only two cases.
9. This operation demands a meticulous and minutely detailed technique.
10. Preoperative and postoperative treatment are essential to a successful end result.
11. The vaginal flap is a protection against postoperative infection and is an excellent procedure for repairing an anterior rectal wall defect.

The illustrations which accompany this article have been prepared by Miss Gladys McHugh.

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4133 MANITOU WAY

DISCUSSION

DR. WILLIAM F. MENGERT, IOWA CITY, IOWA (by invitation).—In 1882, J. Collins Warren said, "The weak point of every operation hitherto devised, lies in the management of the rectal wound." In order to avoid this, Warren suggested the operation which in slightly modified form has given such excellent results in Dr. Campbell's hands.

Although many different procedures have been employed for the correction of this difficulty, it would seem to be highly desirable to select one which avoids concluding with a fresh rectal wound or a suture line internal to the anal sphincter. Bacteria admittedly are present in the rectum despite the most careful antisepsis, and I believe that no suture line, however made, can completely prevent the penetration of organisms into a newly constructed perineal body during the early post-operative course. The vaginal flap operation as practiced by Dr. Campbell avoids the necessity of leaving a fresh wound within the rectum and places all sutures external to the anal sphincter. The same object can also be achieved by mobilizing the rectum, sliding it downward and re-suturing it to the skin margins of a new perineal body, and external to a reconstructed anal sphincter. The origin of this operation has been credited to Marchand, and the procedure is applicable either to a complete perineal tear involving the vaginal and rectal walls or to high recto-vaginal fistulas. In 1902, Noble of Atlanta reported a similar operation, which differed only in the extent of rectal mobilization. Instead of mobilizing the rectum in its entire circumference, only the anterior half is freed and shifted downward. Obviously, this limits the applicability of the procedure to those tears and fistulas which involve not more than the lowermost 3 to 4 cm. of the anterior wall of the rectum.

ceived an excellent anatomic result and were able to control passage of gas and liquid feces. In another patient with a fistula admitting the index finger, the rectum was mobilized in its entire circumference. Subsequently there was separation of part of the vaginal portion of the wound, but the rectal portion remained intact and control of gas and liquid feces was excellent. There were no failures, and adequate fecal control was secured in each of the 11 patients.

It is felt that the essential principle in the healing of wounds of the rectum and sigmoid is adequate fecal drainage. Since the only wound of the rectum following either the vaginal flap operation or the shifting of the rectal wall is external to the anal sphincter, the danger of inadequate fecal drainage is eliminated.

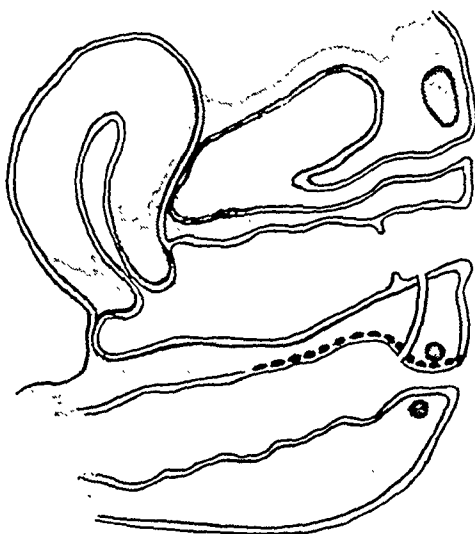


Fig. 4.

DR. FRED L. ADAIR, CHICAGO, ILL.—It is interesting to note that a considerable percentage of the women reported by Dr. Campbell were in the older age group who acquired these tears thirty-two years ago. While in most of these instances the tears are preventable or repairable at the time of delivery, it would be helpful if we emphasized repair at the time of delivery instead of allowing the patients to go for years without treatment.

So far as the operation itself is concerned, the flap method makes a great appeal to operators where it is possible to acquire a sufficient vaginal flap to bring down and cover the vaginal defect. The defect is sometimes too high to secure a large enough vaginal flap to cover the rectal wall. In those cases one has to restore the rectal mucosa with or without a partial vaginal flap.

We should put the third-degree tears in much the same category that we put vaginal fistulas and recognize that they are the result of neglect at the time of labor. I think our efforts should be directed toward the correction of the traditions that lead to these rather than to operation for repair, necessary as that is.

It is of interest to know that in at least some areas the vesico- and rectovaginal fistulas, and also the third-degree tears, are relatively uncommon. The vesicovaginal fistula formerly constituted a major gynecologic problem. Today it constitutes an individual problem, but in some parts of the country the number is relatively small, indicating very definitely that with improved care both of these extremely troublesome conditions can be minimized if not completely eliminated.

DR. CHANNING W. BARRETT, CHICAGO, ILL.—With these tears we should deal with them when they are a few minutes old instead of after thirty or forty years. The tear that leads to the rectum is almost never so far up but that it can be easily mobilized down to the outlet. This does away with any suture line in the anterior wall, does away with scar tissue that always forms along the line of the tear in the rectum, and avoids having some tissue hanging outside of the rectum.

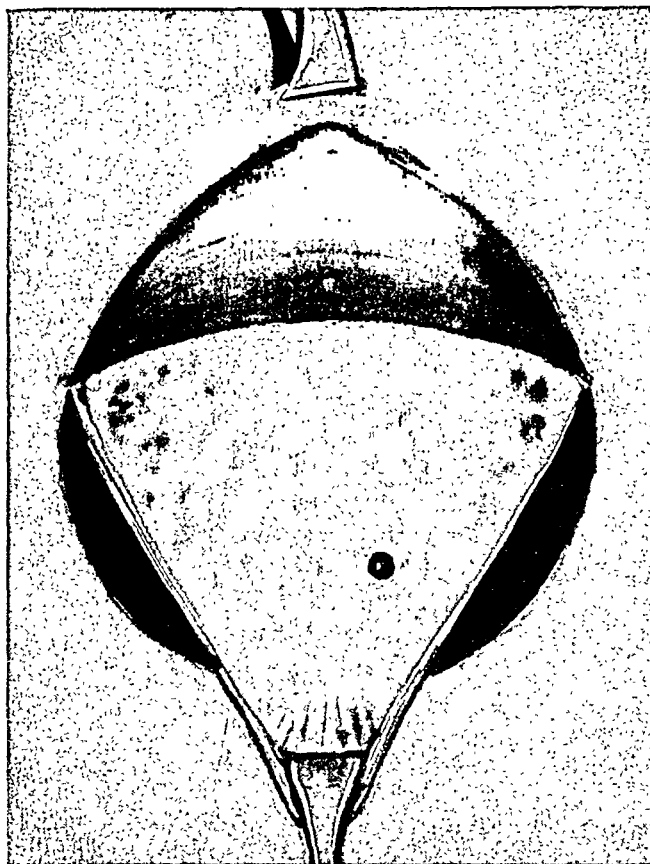


Fig. 2.

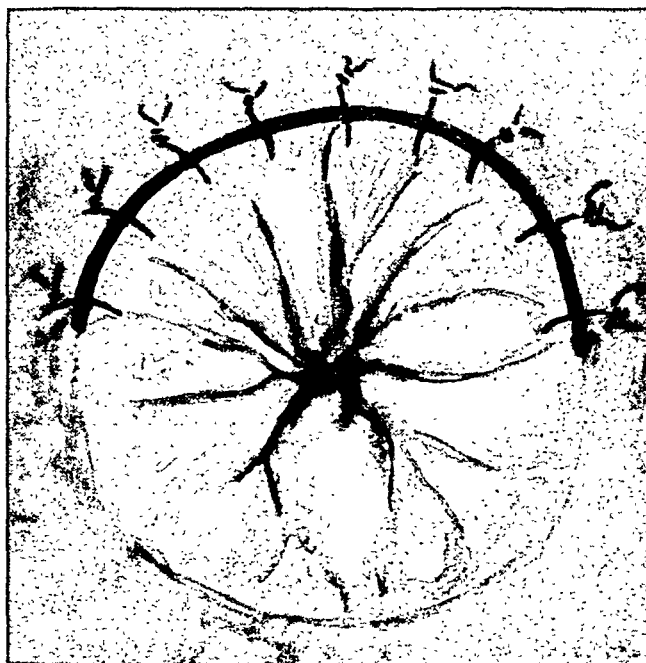


Fig. 3.

ACIDOSIS AND ALKALOSIS IN OBSTETRICS AND GYNECOLOGY*

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THE relation of the alkali-acid ratio of the blood to pregnancy is familiar to every obstetrician. Less familiar is the role of the CO_2 combining power of the blood in the complications and occasional fatalities which occur incident to labor and delivery. In the past, shock and death during or after anesthesia for delivery have been attributed to cardiac thrombosis or pulmonary embolism. From current knowledge of the relation of the toxemia of pregnancy to acidosis, it seemed not unlikely that acidosis might also play a part in these unfavorable developments. Accordingly, in the Department of Gynecology and Obstetrics of the University of Tennessee College of Medicine, in 1938, a series of experiments was carried out in an effort to discover a basis for their occurrence in obstetric and gynecologic practice, and methods of their prevention.

Upon a review of these cases, a conspicuous feature was, almost invariably, a long and severe labor. Bearing in mind a possible association of the two conditions, acidosis and long labor, analyses were made of the urine of a number of patients whose labor was prolonged, and in a few cases acetone and diacetic acid were found. Inquiry as to the reason for this finding revealed that, because of the analgesia, and in order to prevent vomiting during anesthesia, patients were given little food or liquid during the course of labor. The acidosis was therefore assumed to be induced by starvation and dehydration. Forced feedings and the intravenous administration of glucose prior to delivery of all patients in labor over thirty hours has served to eliminate this type of acidosis.

Despite the administration of food and liquids, however, patients still suffered from shock following long labors. Estimations of the CO_2 of the blood were therefore made, not only during the first stage of labor, but also during the second stage and immediately following delivery. It was found that the CO_2 combining power of the blood became constantly lower as labor progressed, the lowest point being reached at the end of the second stage. The highest reading of a group of 192 patients in the first stage was 58 volumes per cent, and the lowest 19.6, the average being 42.98 volumes per cent. The majority, therefore, had a moderate acidosis and a number were in a dangerous state, necessitating careful watching. CO_2 estimations during the second stage of labor in 75 cases revealed an average of 40.05 volumes

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The injury in complete tear is such that scar tissue forms from one side of the rectum to the other, so that the patient has difficulty in holding liquid feces and difficulty in getting rid of solid feces. If we but turn down a flap which retains that scar in the rectum, the patient still has her stricture. That stricture is one of the things that we should dispose of at the time of operation if it is a complete tear.

In a tear that can be made to stretch up so that it looks some distance up the rectum, or can be made to come down outside the rectum, and if that rectal wall is brought to the outlet with a purse-string suture, then we have the sphincter muscle, not in combination with the levator ani as shown in the picture, but as a little facet on each side of the rectum, and the muscle can be drawn out. That muscle should be picked up on the patient's left side, then a bite of the rectal wall taken well enough up so that the end of the sphincter is well above this edge that we have brought down, and then the sphincter on the other side picked up. When that is tied the two ends of the sphincter should come well above the edge in the median line and then the whole technical work is settled. It is only a question then of putting in the right kind of sutures and getting a good result to make it look as if the patient had had no tear and no recent repair.

In those cases with a fistula, if we use the upper edge of the fistula as the upper edge of the septum and split that, bringing the anterior wall down just as we do in a complete tear not having a fistula, it will make the complete closure just as easy as in a complete tear without a fistula. This method makes the repair of a complete tear almost as sure as the incomplete tear of the rectum. And it is a procedure which can be done immediately if the patient has been delivered under proper aseptic precautions, or, if she has not, there is no use adding to the insecurity and danger of the patient by undertaking to do plastic work in that region. It is better to leave the patient with an open perineum than to close up an infected perineum, and do a perineorrhaphy a little later.

DR. CAMPBELL (closing).—Dr. Adair has brought out in his discussion a most important point, namely the prevention of these tears, but one sees the chronic persistent tears as a result of the poor handiwork of someone else, and should know suitable methods of repair in this complication.

In respect to Dr. Barrett's statement that there is a scar bridging across the perineum which hinders good fecal stream control, the patients that I operated upon were checked and rechecked very carefully, and 95 per cent of them had good control of both solid stool and liquid stool. So that so far as any great amount of scarring is concerned in my cases, I did not see it.

unduly prolonged nor severe, the CO_2 was increased, an average of 13.2 volumes per cent, whereas the CO_2 was decreased to 4.4 volumes per cent, on the average, in those having long labor. In the latter, the CO_2 could probably have been increased by larger dosage; this, however, was not thought advisable because of the possibility of vomiting. The necessity for the introduction of sodium bicarbonate by some other means was apparent, yet we hesitated to resort to intravenous or rectal injections without some evidence of the reliability of these methods.

Another experiment was then carried out upon 5 dogs, in which alkalosis was produced by the administration of sodium bicarbonate intravenously. Three of the animals received a 5 per cent solution; 2 of these died. One of the 2 died of alkalosis, as manifested by slowing of respiration and hemolysis, while the other had convulsions. The 5 per cent solution had no effect upon the third. A 2 per cent solution was given the 2 remaining dogs without producing any symptoms. The readings revealed that 1 Gm. of sodium bicarbonate elevated the CO_2 of the blood 7 to 8 volumes per cent. Obviously, a 5 per cent solution was dangerous, in that it produced a too rapid and too severe alkalosis, whereas a 2 per cent solution could be administered with safety.

The above experiment was borne out by the intravenous administration of sodium bicarbonate to 2 ante-partum patients, one of whom received 500 c.c. and the other 1000 c.c. of a 2 per cent solution. In the first, the CO_2 of the blood was elevated 15 volumes per cent, and in the second, 15.3 volumes per cent. Neither suffered any untoward reactions. In addition, 3 patients in labor were given sodium bicarbonate rectally; the CO_2 of the blood was not appreciably altered by this method.

In conjunction with these studies, the effect of sedation on the carbon dioxide-combining power of the blood was observed in 20 cases. Moderate doses of sodium amytal apparently had little effect, probably because a moderate dosage of this drug does not produce sufficient analgesia to limit muscular activity.

In 8 of the 20 patients, the CO_2 was increased an average of 13.1 volumes per cent following sodium amytal, whereas in 12 the CO_2 was decreased 11.4 volumes per cent. When hyoscine was added to the sedation, a definite rise in the CO_2 was noted; this was attributed not only to an intensified analgesia and a consequent diminution of muscular activity but also to better pulmonary ventilation. A few patients who had received sodium amytal and hyoscine were given sodium bicarbonate by mouth, with the result that the CO_2 rose from 4 to 24 volumes per cent, indicating the value of sodium bicarbonate as an adjunct to analgesics.

It has been stated previously that a 1 per cent solution of lactic acid administered intravenously corrected alkalosis in dogs without any adverse effect. In order to verify this observation, as well as the findings from experimental intravenous injections of sodium bicarbonate on acidosis, and to further test the harmfulness or efficacy of these measures, it was thought advisable to reverse extreme states of alkalosis and acidosis in dogs.

In three dogs, alkalosis was produced artificially and then reduced with lactic acid. Two of the 3 were given a 3 per cent solution of lactic acid; both developed hematuria but recovered. This strength would be harmful to the normal dog, but in the presence of the extreme acidosis, caused no damage. A 2 per cent solution would, no doubt, have accomplished the desired result without risk. The third dog of the group had a CO_2 reading of 238 volumes per cent at the time of the lactic acid injection, which, of course, is beyond any clinical alkalosis yet reported. Although we were able to reduce the reading to 82 volumes per cent, the animal died.

To another group of dogs in which acidosis had been produced artificially, sodium bicarbonate was given intravenously in 5 per cent solution. Those with a moderate acidosis had little ill effect from the injections, and it was believed that a 2 per cent solution would have been equally successful. One of the dogs died following elevation of the CO_2 of the blood from 7 to 213 volumes per cent.

per cent, thus showing an intensified acidosis in proportion to the duration and character of labor. The studies made after delivery revealed an average CO_2 of 48.9 volumes per cent, indicating a prompt return to normal. From these findings, it was assumed that the increasing acidosis of the second type was induced by muscular activity and a consequent accumulation of lactic acid in the blood.

To substantiate these observations, it was decided to test the effect of lactic acid upon the CO_2 of the blood. Solutions of 3, 2, and 1 per cent were given intravenously to a number of dogs, with the result that those which received the 3 per cent solution developed hemoglobinuria, respiratory disturbances, and occasionally vomiting, and died. Those given a 2 per cent solution had a mild hemoglobinuria, but recovered, while those given the 1 per cent solution suffered no apparent harm. One gram of lactic acid reduced the CO_2 of the blood 4.3 volumes per cent.

Pursuing this study, another group of dogs was given ether for varying periods, the average being twenty-five minutes, and CO_2 readings were taken at the end of the anesthesia. In none of the animals was the anesthesia carried to the end point; even so, an average decrease of 7.3 volumes per cent in CO_2 was shown. This was in conformity with previous observations that anesthesia produces and intensifies acidosis.

These findings seemed to confirm our theory that the diminished CO_2 combining power of the blood is a significant factor in obstetric complications and fatalities. In order to combat the severe acidosis of prolonged labor, therefore, it was decided to administer sodium bicarbonate to patients who failed to respond to glucose and insulin. Our first experience with this procedure was an unfortunate one. A patient was admitted to the hospital after having been in labor for five days. She was in a state of extreme shock; her blood pressure was low, her pulse rapid, and her skin cold and clammy. No acetone nor diacetic acid was found in the urine, but the CO_2 of the blood was only 15 volumes per cent. Glucose and insulin were administered, without effect. Accordingly, a 2 per cent solution of sterile sodium bicarbonate was given intravenously. The CO_2 of the blood promptly rose and the patient's immediate reaction was favorable. Subsequently, however, she had a relapse and died.

From this experience, it was believed that the combination of glucose and sodium bicarbonate gave rise to a chemical incompatibility which was lethally toxic. This theory was tested by an experiment upon eight dogs. A state of acidosis was first produced in the animals by etherization, and a combination of 10 per cent glucose solution and 5 per cent sodium bicarbonate solution was then given intravenously; all were seized with convulsions and died.

Since sodium bicarbonate had been used successfully in the control of the acidosis of uremia, it was still felt that without glucose or insulin it would have a similar effect upon the acidosis of labor.

Consequently, sodium bicarbonate was given in one-dram doses by mouth to 20 patients during normal labor, the acidosis of dehydration and starvation having first been precluded by food and liquids. In those patients whose labor was not

The acid base disturbance in pregnancy is due to a reduction of total base and not to the accumulation of abnormal acids, and accordingly it has been more correctly termed a compensated alkaline deficit. In eclampsia, however, at the time of convulsions and coma, a true acidosis exists from the accumulation of acids incidental to the muscular work of the convulsion.

Our common clinical experience has shown the value of fluids and glucose in preventing dangerous exhaustion, but Dr. Pride's findings show the ever present potential dangers when the phase approaches an uncompensated CO_2 excess due to lactic acid production, an acid base disturbance where glucose and insulin would naturally be ineffective. The ability of the tissues to handle lactic acid is, however, such that one would expect them to metabolize it between muscular contractions unless the patient suffered from anoxemia. Before the stage of decompensation, even saline tends to safeguard the alkali reserve if the kidneys continue to secrete normally ammonium chloride and acid phosphate.

When the pH of the blood is seriously threatened, however, intravenous sodium bicarbonate therapy would appear logical. One, however, must be on guard against the use of sodium bicarbonate without laboratory control, as an overdose may lead to an alkalosis which is just as dangerous as an uncompensated acidosis. According to Palmer and Van Slyke, to raise the plasma CO_2 one volume per cent requires about 0.026 Gm. of sodium bicarbonate per kilo. In a 60 kilo patient, 1.56 Gm. of sodium bicarbonate would increase the CO_2 by only one volume per cent and 15.6 Gm. only 10 volumes per cent. If one were to give 10 Gm. (500 c.c. of 2 per cent), the effect on the plasma CO_2 would be small and one would think hardly worth while (only about 6 volumes per cent).

At the Toronto General Hospital it has been demonstrated that 500 c.c. of 5 per cent sodium bicarbonate may be given by intravenous drip over a period of two hours without obvious ill effects and with symptomatic improvement. It has been given during the course of administration of glucose to patients in diabetic coma, end-stage nephritis, some cases of leucemia, as well as one case of hyperthyroidism in which postoperative acidosis was severe. Given carefully it appears to be a safe procedure in cases of severe acidosis.

It is also noteworthy that a gradually accumulating acidosis during a long labor is per se a more dangerous phenomenon than the more transitory eclamptic condition, especially if in addition to the other signs of exhaustion supervening, renal deficiency develops.

DR. PRIDE (closing).—Replying to the question, what strength and amount of lactic acid should be given: After much experimenting, we found 1 per cent was safe. This can be given up to 500 c.c. solution, depending upon the patient. Stronger percentages gave trouble. The CO_2 combining power must be checked before giving the solution.

The 1 per cent sodium bicarbonate is entirely safe up to 500 c.c.

The sudden deaths occurring under anesthesia can be reduced to a minimum if this procedure is followed.

These studies, apparently, have not only explained the role of prolonged labor and acidosis in shock in obstetric cases, but they have likewise revealed a similar association of alkalosis to many puzzling problems in both obstetrics and surgical gynecology. Although alkalosis is rarely observed in obstetric practice and only occasionally in gynecologic operations, the condition can be no less dangerous than acidosis. Early manifestations are the slowing of respiration, an increase in the CO_2 volume of the blood, hemolysis of the corpuscles, venous congestion, and, in some cases, convulsions.

We have encountered alkalosis in 3 gynecologic patients following rather prolonged gas anesthesia. All 3 were apparently in good condition prior to the operation. Soon afterward, the first patient presented the symptoms of shock, which we assumed was induced by an acute acidosis from the prolonged anesthesia, especially since there was no diminution in urine secretion. She was therefore given normal saline by vein, without effect, and one hour later a blood transfusion, also to no avail. Thereupon, an investigation revealed a CO_2 combining power of the blood of 78 volumes per cent.

The other 2 patients had rather extensive pelvic operations, but were in good condition after the rectal administration of normal saline by the drip method. Several hours later, however, they were reported to be in a state of shock, and when the CO_2 of the blood was estimated, both were found to have a severe alkalosis, rather than an acidosis, as was suspected. Neither patient had vomited, though the pelvic disease was conducive to a lowered vitality.

All three of these patients were observed prior to our experimental work. A 1 per cent solution of lactic acid probably would have corrected the alkalosis had it been recognized before the operation.

In view of the findings from the above experiments, we have felt no hesitancy in administering 1 per cent solution of lactic acid intravenously to patients suffering from alkalosis, or sodium bicarbonate in 2 per cent solution, intravenously, or in hourly dram doses by mouth, to those threatened with the physiologic acidosis of labor. In every case, medication has been regulated according to repeated CO_2 readings. The results have been uniformly gratifying. Since beginning this practice, we have encountered retraction rings in 6 patients; in 2, the rings were promptly relaxed by sodium bicarbonate injections and the deliveries were carried out without further difficulty. We now believe that acidosis and alkalosis can be combated in obstetric and gynecologic procedures if the condition is recognized early, and these measures are carried out under the control of estimations of the CO_2 combining power of the blood at necessary intervals. It should be borne in mind that the combination of sodium bicarbonate and glucose for the correction of acidosis is to be avoided, in that, together they give rise to a chemical incompatibility which is lethally toxic.

DISCUSSION

DR. H. B. VAN WYCK, TORONTO, CANADA.—Some years ago, on Dr. Hendry's service at the Toronto General Hospital, an attempt was made to anticipate dangerous exhaustion by estimation of the CO_2 combining power in any labor prolonged to thirty-six hours. This was not continued, because with the more routine employment of the usual preventive measures, we believed that we were successfully insuring the patient against dangerous exhaustion. In the last twelve months, however, we have had two deaths in the category under discussion.

therefore, we describe, consider, and repeat this important point. Students should know that dilatation of the cervix begins at the internal os and progresses to the external os, and the result of this process is called effacement. As the cervix is effaced, it is retracted slowly but surely over the presenting part, and that sometimes in a primipara, little or no dilatation of the external os may occur until only a very thin portion of the cervix is left. They must know that this process of dilatation, effacement, and retraction, is the physiologic process of labor, and not until the cervix is fully retracted is the first stage of labor complete. A failure to recognize this normal process in some cases may lead to meddlesome obstetrics.

It is in home deliveries that medical students learn the most about normal obstetrics. It is here that they develop confidence in themselves, take measure of their own ability, and visualize for the first time, actual occurrence of presentation, position, and mechanism of labor. I wonder if students would not like to say, "Don't give us a lecture to learn obstetrics, but give us a case in the home to deliver."

We advise our residents, whose position should be recognized, not to be too familiar or patronizing with the students, just a friend and a teacher, for students are cooperative and responsive to suggestions from competent residents, and from the teaching faculty. Caution should be exercised in selecting residents who have the ability, personality, and character, and who are interested in teaching clean and efficient obstetrics whether it be in the home or in the hospital. We like our residents to have that uncommon gift of common sense.

The students take full charge of the deliveries but are responsible to and under the supervision of the resident. Any abnormal findings must at once be reported to the resident, and if the residents are not available, then to one of the dispensary obstetricians on service at the time. All major pathologic cases who visit the antenatal clinic, or develop complications before or at the time of delivery, are admitted to the hospital for further care, study, and delivery. Only non-complicated cases are delivered in the home.

A complete record on each case must be submitted by the student to the resident within ten days after the service is completed. These records are marked "poor," "good," or "excellent," by the resident, received by the Dean, and are considered in the student's final grades.

Home Delivery Service is limited to senior students who serve in pairs, and who have the privilege of selecting their own partners. The pairs of students serve in sequence for a period of seven days, on each service through the following assignments: (a) Prenatal Clinic, (b) Parkland (city, county) Hospital, (c) Home Delivery Service (second call), (d) Home Delivery Service (first call).

The prenatal clinic is held daily from 10:00 to 12:00 A.M. in the hospitals. Cases are assigned to the students for history, physical examinations, laboratory tests, and when completed, the charts are presented to the instructor for discussion and for a check of the students' findings.

HOME DELIVERY SERVICE FOR MEDICAL STUDENTS*

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(From the Baylor University Obstetric Service)

THE preparatory training for home deliveries begins as an introductory course of eleven hours, one hour per week during the third trimester of the sophomore year. This course embraces a general review of the anatomy of the pelvis, pelvic peritoneum, the perineum, the reproductive organs, and the physiology of the endocrines in relation to gestation.

The instruction in the third year consists of a total of eighty-five hours, three one-hour didactic periods per week during the third trimester. During the fourth year, the class is divided into sections, and a total of thirty-two hours is devoted to the study of case records of the deliveries made by the students in the home and the hospital. The student who made the delivery presents this record which includes a complete history, physical and laboratory findings, and history of previous pregnancies and deliveries including this delivery. We encourage the student to admit his errors in his reports, as this is a wholesome mental attitude for both the student and the teacher. The case is then considered by the class and studied as in a pathologic clinical conference.

The teaching in all courses is largely by the question and answer method, discussions, and manikin demonstration, rather than by formal lectures. From this method of teaching, it is gratifying to see members of the class anxious to express their ideas and to pool their information with that of the teacher and their fellow students. Class discussions rather than lectures are more effective and instructive, for facts are fixed in the students' minds by discussion.

In teaching the signs and symptoms of pregnancy to our Junior Class, we try to show why the physiologic changes are present. Why is the diagnosis of pregnancy so difficult to make in the early weeks? Why are there so many modified Friedman and Aschheim-Zondek tests for pregnancy? Is it due to our methods of teaching? Hegar's sign is a positive sign of pregnancy and to recognize this sign requires clinical experience. The place to teach Hegar's sign is in the prenatal clinic where patients in early pregnancy come for diagnosis and instructions. When found to be pregnant, we ask the patient to return frequently in order that students may make bimanual vaginal examinations to familiarize themselves with this physiologic growth and this change in the uterus. We impress the fact that it is necessary for the bladder to be empty to make this examination, a too often neglected procedure.

We know that many errors in a normal delivery are due to the lack of knowledge of the physiologic mechanism of the first stage of labor,

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part of a utility nurse. The medical student who is serving as a nurse, places an ironing board under the mattress for support and prepares the table for sterile drapings and supplies. The student who is making the delivery has scrubbed his hands, dried them, and has put on his sterile gown and gloves. Draping of the patient is as follows: The assisting student lifts the patient up, and a large sterile sheet is placed over the bed and under the patient's buttocks. The legs are still held so that sterile boots, which are long enough to extend to the vulva, can be slipped on the patient's legs. A sterile sheet is placed over the abdomen, with towels placed over the abdominal spread and over the top of each boot. The towels on the boots are held by rings. During the delivery, a towel is used to protect the anus. Immediately after the patient is draped, the bladder is emptied. If the patient is in the second stage of labor, she is told to bear down during the uterine contraction, at which time the assisting student gives the patient chloroform. In the delivery of the head and during a contraction, a moderate pressure is made on the vertex of the baby to prevent a too rapid extension and expulsion which we believe is a more effective way to prevent injuries to the baby and lacerations of the perineum. Chloroform is used, and is given at the beginning and for the duration of the uterine contractions, and then removed and not given after the delivery of the head. Slow delivery and gentleness in delivering the head and shoulders of the baby are advised, and at no time is traction put upon the head. The baby is dried with a towel, the mucus aspirated from the throat, and when this is completed, 1 per cent silver nitrate solution is placed in the baby's eyes. Under ordinary conditions, the cord is not ligated until pulsation stops, as we sometimes think the baby may receive a little more blood from the placenta, and more time is given for the separation of the placenta. The baby is laid aside in a warm blanket and later cared for by the assisting student.

Attempt at delivery of the placenta is not made until the fundus of the uterus has ascended above the umbilicus, and then during contraction, gentle pressure by Credé method is made. Upon delivery of the placenta, the membranes are best detached by pushing the uterus further up into the abdomen while gentle traction is made on the placenta. We do not use the various methods of twisting or pulling on the placenta, because we feel that this may account for retention of membrane and elevation of temperature in the puerperium. The field of operation is cleaned, and peri-pads with T-binders are applied. After forty-eight hours, all dressings are removed and pads placed beneath the buttocks for drainage. No other dressings are applied. Soap and water are used externally for cleanliness.

The patient is advised to change position frequently and to make herself comfortable. A general diet is permitted and mineral oil is used after the second day. Instructions concerning lactation are given, and she is taught that the mammary glands are organs of secretion and not reservoirs. We do not credit a rise of temperature to engorgement of the mammary glands, but should elevation of temperature occur, it is probably due to puerperal infection. Daily post-partum calls are made by students for the first five days, then every other day until the tenth day, then as indicated.

STATISTICAL RESULTS

From July 1, 1937, to March 1, 1939, 4,000 consecutive deliveries in the Obstetrical Service in Baylor University Hospital, Florence Nightingale division, were made: 44.4 per cent, or about 1,700, were patients delivered by private physicians, 55.6 per cent, or about 2,300 were on the charity service, 436 of which were delivered in the hospital. A rise of temperature to 100.4° F., or above, for two or more consecutive days occurred in 94 charity cases in the home and hospital. It was found that temperature elevations occurred most frequently in those patients who had prolonged labor, with some type of operative obstetric procedure necessary for the termination of labor.

There were four maternal deaths on the charity service and none in the private service. The causes of the deaths were two cerebral hemorrhages following labor

During the Parkland Hospital Service, the students live in the hospital, do their clinical clerkship, observe the progress of labor, and assist in the deliveries under the direct supervision of the members on the obstetric staff.

In order to receive the obstetric calls for the students, a twenty-four-hour telephone service for home deliveries is maintained through Baylor University Hospital. Patients are cared for in all parts of the city, including two smaller adjoining municipalities and at times outside the city limits within reasonable distance. Students furnish their own automobile transportation, but obstetric bags completely equipped are supplied through the university outpatient department. Before entering upon the home delivery service, the resident gives individual instructions to the students concerning preparation and draping of the bed and patient before delivery.

Under the supervision of the resident, the students are responsible for all phases of the delivery in the home, from the first steps in the preparation and draping of the patient on through the actual delivery, post-partum care, and care of the infant. We do not have the finances to employ nurses for this service, but we believe it is of benefit to the student to assume the duties of a nurse in order that he may better know his responsibilities and learn to appreciate clean obstetrics. It is our purpose to make the home delivery service so thorough, practical, and efficient, that the student will on graduation know that the delivery of a baby is a physiologic process, and rarely is operative interference necessary. If necessary, it should have been recognized during the antenatal period.

When students receive calls, they promptly go to see their patient and make the following observations and preparations:

1. Take a history—inquire as to the frequency and duration of uterine contractions.
2. Determine position and presentation by abdominal and by rectal examinations, and estimate the amount of effacement and dilatation.
3. If time is sufficient, an enema is given.
4. After a physical and obstetric examination, a first preparation is done by shaving and washing the perineum with tincture of green soap.
5. An abdominal buckle binder is applied.

The student remains in the home with the patient and observes the frequency, intensity, and duration of uterine contractions, and records his findings. During the course of ensuing labor, careful check of her progress is made by rectal examinations at frequent intervals, and the student reports his findings to the resident.

The preparation for delivery of a primipara is made when the head begins to crown, and usually in a multipara when effacement and dilatation of the cervix is 8 to 10 cm. This information is ascertained by rectal examinations made by the student, and one marvels at the aptness of the student to grasp this situation. Our preparation in the home is about the same routine as we use in the hospital. The field of operation is again cleaned with soap and water, sponged with alcohol, and one-half strength tincture of iodine is applied. The patient is then draped. During this preparation, one student scrubs his hands while the other takes the

perhaps with certain details in his procedures, such as the conduct of the third stage and the use of chloroform as an analgesic. But these are matters of opinion. The maintenance of asepsis is admirable, but one may wonder whether the local application of alcohol and half strength tincture of iodine is tolerated by a wide awake patient without objection. I would also like to ask how many deliveries are made as an average for each student, for numbers count when practical experience is to be evaluated.

Notwithstanding the drift to hospitals, many women for years to come necessarily will be confined in their homes by their family physicians. It is well for the physicians to know how it may be done with safety for their patients and with credit to themselves. I feel that the example set by Dr. Hannah and by others who are engaged in this work, deserves our commendation and not the reproach which is sometimes meted out to them in certain quarters that shall be left nameless. It would be of interest and value to have a country-wide study made of the general scope and the results obtained in these student obstetric services. Perhaps this Association may be prevailed upon to undertake the task.

DR. GRANDISON D. ROYSTON, ST. LOUIS, MO.—Ample hospital facilities are usually available in urban areas. Eighty-five per cent of the births in St. Louis during the past year occurred in hospitals.

In the Washington University Clinic we attempt to deliver in the hospital *all* primiparas and those multiparas with any complication. Six or seven years ago, we had about 425 home deliveries per year, but for the past three or four years the number has ranged from 163 to 181 per year. Smaller communities and rural districts have a larger proportion of home deliveries. In some of these, the small poorly equipped hospital may be less desirable than the home for the delivery of normal cases.

Are medical schools preparing their students to care safely for these home deliveries? The present tendency to minimize their necessity would seem to invite or encourage in the students a careless indifferent attitude toward their importance.

Dr. E. T. Bruning, of Santa Ana, California, emphasizes that the present lethargic attitude of the medical profession toward the importance of home deliveries has been due to lack of proper equipment. Schwarz and Bruning developed a 35-pound portable delivery table, known as the Washington University delivery table. We have employed this table satisfactorily in the Washington University home delivery service for the past three years. Bruning has also developed a set of paper drapes that can be sterilized for one hour in the autoclave under 20 pounds' pressure. These are not opened until the patient is ready to be draped, and are burned immediately after use. This minimum handling lessens the dangers of infection that may be communicated through the laundry or attendants, in case of washable cloth drapes. Washable cloth drapes are often too few or too thin to offer reliable protection after they are once wet, while the paper drapes are less permeable and have had no contact with other drapes.

This discussion is not to be construed as advocating a preference for home over hospital deliveries. It is a plea for preparation of medical students in obstetrics, so that they can do safe work wherever they may be called, and many of them can profit by being taught ordinary surgical cleanliness and adaptability in home deliveries.

DR. IRVING W. POTTER, BUFFALO, N. Y.—I agree with Dr. Hannah in what he has said on what the average doctor seems to know about the beginning of labor. The men with whom we see cases are divided into two classes. The first class are those doctors whose patients are usually not in labor when we are called. We generally go at once to the second group of men because they need help, and usually have waited too long with the more complicated cases. There are plenty of men doing obstetrics who attempt to deliver a woman who is not in labor. It is very important to recognize the effacement of the lower uterine segment and important to know when it is complete, also when the os is dilatable. An opening that you can put your finger in with no effacement does not mean an immediate delivery.

in hypertensive cases, one fulminating toxemia, and one puerperal infection. In the 4,000 cases we had 59 cesarean sections, 5 in the charity, and 54 in the private cases.

Of 1,364 cases on our charity service from July 1, 1939, to June 30, 1940, 212 were delivered in the hospital and 1,152 in the home. Those delivered in the hospital showed one puerperal infection; one maternal death occurred in a patient who had paresis and died suddenly during labor. Those delivered in the home showed 4 puerperal infections. There were three cesarean sections out of 1,364 cases.

CONCLUSION

A home delivery service for the student does not retard initiative and resourcefulness, but stimulates independent growth. This course teaches that one should not become too dependent on the hospital amid comforts, but that the hospital is the fort for cases of complication. We teach that pregnancy and labor are normal processes, and by being clean and conservative, it can still be done safely in the home.

DISCUSSION

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—The steadily increasing hospitalization of women for labor might make it appear as if the instruction of medical students in home deliveries is no longer necessary in this present day and age. Estimates have been made which show that during the last twenty years institutional births have mounted in some of our large cities to as much as 80 per cent of the total number of deliveries. It might prove an ideal situation if the advantages of a hospital delivery could be accorded to all pregnant women.

One may be inclined to doubt, however, this claim that universal hospitalization would be completely ideal; for we find that the triad of fatalities included in hemorrhage, toxemia, and sepsis claims perhaps as many victims in the hospitals as in the homes. And to what may this be ascribed? There is widespread, although perhaps somewhat mistaken, belief that a hospital spells safety but this, in a sense, is far from the truth. It is the character of the hospital which is the deciding factor, for not all hospitals so-called are necessarily good hospitals. Moreover in the country at large there are not enough institutional beds available to provide ideal conditions for all our pregnant women. The supposed advantages of a hospital confinement also carry in their train an increased incidence of operative deliveries, interferences with the normal processes of labor, indiscriminate employment of methods of pain relief, and the loss of that important virtue of the obstetrician, namely the exercise of patience. I would not decry for one moment the convenience of hospital deliveries, both for the patient and the physician, but to claim that the institution is the sole recourse is to indulge in an exaggeration.

The foregoing remarks may seem a divergence from Dr. Hannah's presentation. However, I make them as an endorsement of his thesis that a home delivery service is an essential factor in the training of our medical students, in order to cultivate their self-reliance and their practical application of theoretic teaching. In no other way can the gap between theory and practice be bridged so successfully. The observation of a delivery in a well-equipped hospital operating room is very desirable, but it fails to engender in the student that respect for the patient and her environment, that close contact through the waiting hours, that necessary reliance on his personal ability and perhaps conscience. All of these are essential to his success as an obstetrician. He is taking care of Mrs. Jones in the tenement house and not a case from Ward B.

Dr. Hannah has done a good service in calling renewed attention to the value and success of an out-door obstetric teaching service. He stresses the adequate preparation and close supervision of the students. He points to the desirability of an association between the out-door service and a hospital, and the record of morbidity and mortality in his institution is an enviable one. One may differ

but we believe home delivery is a better way to teach clinical obstetrics. We deliver approximately 100 patients per month in Parkland Hospital, probably 25 patients in Baylor Hospital, and 80 to 110 patients in the homes. This is a fair estimation of our charity work in the Obstetrical Department of Baylor University College of Medicine. Each of our students will deliver from 35 to 50 patients before graduation and quite a number of them may deliver more. It is interesting to see how proud the student is when he returns from a successful delivery, even though he has spent hours on the case. It is the responsibility; it is the anxiety; it is the moral support given to the student by his resident and staff members during a home delivery that teaches him that pregnancy and labor can still be conducted safely in the home.

Obstetric departments of medical schools are fully aware of the difficulties of teaching obstetrics as compared with the teaching of medicine and surgery. In these branches the clinical material is hospitalized and complete preparation of the patient is made for the clinician and a definite time is arranged for the students and the teachers, while in obstetrics the irregular hours and the indefinite time of delivery cannot be arranged. Medical students should be required to make home deliveries that they may better learn that the development of a mental attitude towards the practice of medicine is acquired through responsibilities and the experience of anxious hours.

NATIONALITY AND CARCINOMA OF THE CERVIX*

FRANK R. SMITH, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Gynecological Service of the Memorial Hospital)

REALIZING that poverty and multiple parturition are constant factors in carcinoma of the cervix, I¹ (in 1928 to 1930) attempted to find additional factors by personally interviewing 226 patients suffering with cervical carcinoma, and by comparing this group with a comparable number of noncancerous patients selected as controls because of their age, multiparity, and similar economic status. Several possible additional factors were found. The comparison of the two series as to nationality (reproduced as Table I) was passed over rather briefly as having little significance.

TABLE I. COMPARISON OF THE TWO SERIES AS TO NATIONALITY

NATIONALITY	CARCINOMA		CONTROL	
	NO.	%	NO.	%
Black	20	8.8	31	15.3
White	206	91.1	171	84.6
German	20	8.8	17	8.4
Italian	74	32.7	30	14.8
Jewish	15	6.6	33	16.3
Greek	2	0.8	0	0.0
Irish	45	19.4	52	25.7
Polish	8	3.5	3	1.4
Others	42	18.5	36	17.8
Total cases	226		202	

Horwitz² had previously reported that at the Mayo Clinic the disease was only one-fourth as frequent in Jewesses as in Gentile women. While

*Read at the Fifty-Third Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Excelsior Springs, Mo., September 26 to 28, 1940.

DR. JAMES L. REYCRAFT, CLEVELAND, OHIO.—We have a very large service in Cleveland under our direct supervision. The out-patient deliveries at the Maternity Hospital are done by the students and amount to about 2,000 a year. We have 1,500 a year on the in-service at the Cleveland City Hospital, and in addition about 100 cases a month on the in-service at the Maternity Hospital.

I want to emphasize the matter of supervision. If you can have an organization that gives adequate supervision, it makes for better obstetric habits. A student is going to learn more about obstetrics in the long run if he is very closely supervised. We allow them to see deliveries in the hospital, and when they go on a case in a home they are permitted to make a vaginal examination to determine the progress of the case and whether the measurements are adequate. The patients in whom difficulty is expected are sent to the hospital. If the student finds the case is a normal one, usually a multipara, he makes an examination and reports in. When the patient has progressed normally and is near to delivery, the assistant resident goes out. He is directly responsible to the resident, who in turn is responsible to one of our visiting obstetricians. A delivery nurse is usually present. We require twelve deliveries by these men and they usually get from twenty to twenty-five deliveries on their out-patient service.

DR. WARD F. SEELEY, DETROIT, MICH.—It is true that a large percentage of deliveries, at least in the rural districts, do occur in the home. The same is true for most cases of measles, fractures, pneumonia, etc., but no other department of medicine feels that it is necessary to go into the home and teach their students at the bedside. I think our attitude is a hold-over from the time when we did not have hospital facilities sufficient to teach medical students and therefore had to carry our teaching into the homes of the patients.

I agree that a student is probably a better obstetrician after having had the experience of a home delivery service, but I also believe that he first should have had his experience in the hospital and that adequate supervision should be provided in order that he does not make the same mistake time after time without correction. I believe that this supervision should be provided for by sending him out with an instructor rather than with a resident.

I disagree with Dr. Hannah on the matter of equipment. I think the student should be sent out with a minimum of equipment. We do not attempt to carry the hospital to the patient but rather to teach our students to work aseptically with material and under conditions as they will find them in actual practice.

DR. HANNAH (closing).—Dr. Kosmak has asked a question about the giving of chloroform by our students in home deliveries. We believe that chloroform in labor, if carefully given and the patient not too rapidly and deeply anesthetized, is comparatively safe. We are fully aware of the danger of the use of chloroform, and the students are so taught. Had we the financial means we would probably use nitrous oxide gas.

We do not have nurses to accompany the students on home deliveries. Nurses are an excellent asset for this work, but we have learned the educational value to the medical student who assumes the duties of a utility nurse. What better way have we to teach than by actual doing? The student who makes the delivery scrubs and prepares himself as the obstetrician who makes a delivery in the hospital, while his co-worker acts as a utility nurse and anesthetist. Our students are taught to report every hour, or every two hours, to the resident, and more often if in doubt as to the progress of labor. Our residents are expected to go to the student's aid, and if they find complications or are in doubt as to the prognosis, the patient is brought promptly to the hospital. In home deliveries, if the occasion arises, we permit our residents to apply low forceps when the head is arrested on the perineum, do episiotomy and repair. Forceps in this sort of case is usually applied without any anesthetic and traction is made only during uterine contraction, at which time a few drops of chloroform may be given.

We teach that the student, resident, and the staff doctors should not take anything for granted. We, as others, would enjoy the comforts of hospital facilities,

The Italian, Irish, and Scotch-English groups appear in this order of frequency, with Jewesses having an even smaller incidence than in the smaller group. Having found in the continuation of this study an Irish-Catholic married to a man named Cohen and classified as a Jewess, this presentation was held up from 1937 to the present date in order personally to question the living patients suffering from cancer of the cervix as to their race and nativity. The error of race and nationality as filed was found to be less than 0.1 per cent and, therefore, negligible.

TABLE IV. COMPARISON OF PERCENTAGES OF NATIONALITY INCIDENCE IN THE SEVERAL TYPES OF GYNECOLOGIC LESIONS

	CERVIX	CORPUS	OVARY	VULVA	BENIGN	CLINIC	
	%	%	%	%	%	NO.	%
Black	7.2	3.1	1.8	4.3	7.8	426	6.9
German	10.9	7.6	5.4	6.0	8.1	582	9.4
Italian	16.9	7.1	4.0	8.6	8.6	777	12.5
Jewish	4.2	19.6	21.6	7.8	35.5	1085	17.5
Greek	0.3	0.0	0.0	9.0	1.4	43	0.06
Irish	13.4	18.6	3.1	15.6	15.8	890	14.4
Polish	1.0	0.4	0.0	0.8	3.0	104	1.6
English and Scotch	10.6	0.0	4.9	0.0	8.6	439	7.1
Austrian	3.3	2.6	7.2	4.3	3.2	219	3.5
U. S. A.	24.5	35.2	40.7	50.4	5.6	1191	19.3
Others	6.7	5.6	5.4	1.7	1.0	412	6.6
Total	3106	445	221	115	2281	6168	

Comparison of the total primary cervical carcinoma incidence with the other individual lesions and with the total cross section of the clinic shows the Italian and Scotch-English groups to be considerably higher in the cervix group than in the other groups. The Irish incidence is about the same in all groups. The Jewish incidence in the cervix group is strikingly low by comparison with the other individual lesions and with the clinic cross section. The German incidence is slightly higher in the cervical group. Since the cervix cases are more than half of the total cases studied and this being a perhaps undue influence on the total clinic cross section figures, these two classifications have been compared with the total noncervical lesions used, and the results are shown in Table IV A.

TABLE IV A. COMPARISON OF NATIONALITY INCIDENCE IN PATIENTS WITH CERVICAL AND NONCERVICAL LESIONS AND WITH A CROSS SECTION OF THE ENTIRE CLINIC

	CERVIX		CLINIC		NONCERVICAL	
	NO.	%	NO.	%	NO.	%
Black	225	7.2	426	6.9	201	6.5
German	341	10.9	582	9.4	241	7.8
Italian	528	16.9	777	12.5	249	8.1
Jewish	132	4.2	1085	17.5	953	31.1
Greek	10	0.3	43	0.06	33	1.0
Irish	419	13.4	890	14.4	471	15.3
Polish	32	1.0	104	1.6	72	2.3
Scotch and English	330	10.6	439	7.1	109	3.5
Austrian	104	3.3	219	3.5	115	3.7
U. S. A.	764	24.5	1191	19.3	427	13.9
Others	221	7.1	412	6.6	191	6.2
Totals	3106		6168		3062	

cancer of the cervix was known to be prevalent among Italians, their relatively large proportion in the cancer series was dismissed on the assumption that Memorial Hospital had a large Italian clientele.

TABLE II. COMPARISON OF NATIONALITY IN SELECTED GROUPS CLASSIFIED AS TO DIAGNOSIS

NATIONALITY	CARCINOMA OF CERVIX		CARCINOMA OF CORPUS		CARCINOMA OF OVARY		CARCINOMA OF VULVA		BENIGN	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Total	226		445		221		115		2,273	
Black	20	8.8	14	3.1	4	1.8	5	4.3	178	7.8
White	206	91.1								
German	20	8.8	35	7.6	12	5.4	7	6.0	187	8.1
Italian	74	32.7	32	7.1	9	4.0	10	8.6	198	8.6
Jewish	15	6.6	85	19.6	47	21.2	9	7.8	812	35.5
Greek	2	0.8	0	0.0	0	0.0	0	0.0	33	1.4
Irish	45	19.4	83	18.6	7	3.1	18	15.6	363	15.8
Polish	8	3.5	2	0.4	0	0.0	1	0.8	69	3.0
English	0	0.0	0	0.0	11	4.9	0	0.0	198	8.6
Austrian	0	0.0	12	2.6	16	7.2	5	4.3	82	3.5
Others	42	18.5	25	5.6	12	5.4	2	1.7	25	1.0
Not recorded	0				13	5.7				
U. S. A.	0	0.0	157	35.2	90	40.7	58	50.4	128	5.6

In an attempt to compare the nationality incidence in cervical cancer in this series with that of patients suffering from other gynecologic lesions, consecutive records as filed have been studied, but the numbers used in each classification are not the entire number of patients filed under that diagnosis; i.e., this is a cross section of the clinic in the years studied rather than the total number of cases in the clinic. The high Italian and low Jewish incidence in cancer of the cervix as compared with that of the other gynecologic lesions is the outstanding feature of this study. Since the carcinoma of the cervix series only included patients who gave the opportunity for personal interviews, the number was necessarily small. For this reason it seemed advisable to study all the records of patients having primary carcinoma of the cervix, and who were treated at Memorial Hospital from 1916 to 1937. The 3,106 patients studied are classified as to nationality in Table III.

TABLE III. TOTAL CERVIX CASES CLASSIFIED AS TO NATIONALITY

NATIONALITY	NO.	%
Black	225	7.2
German	341	10.9
Italian	528	16.9
Jewish	132	4.2
French	54	1.7
Irish	419	13.4
Polish	32	1.0
English and Scotch	330	10.6
Austrian and Hungarian	104	3.3
Dutch, Spanish, Belgian, Japanese, Swiss, unclassified	91	2.9
Greek	10	0.3
U. S. A.	764	24.5
Danish, Swedish, Finnish, and Norwegian	76	2.1
Total	3,106	100.0

TABLE VI. COMPARISON OF NATIONALITY INCIDENCE (EXPRESSED IN PERCENTAGES) OF FIVE-YEAR PERIODS AND TOTALS IN CARCINOMA OF THE CERVIX

NATIONALITY	1915-20	1921-25	1926-30	1931-35	1936-37	TOTAL 1915-37	
						NO.	%
Black	3.0	6.1	7.2	8.9	10.8	225	7.2
German	10.7	9.8	12.0	11.1	10.8	341	10.9
Italian	15.5	16.6	17.0	15.9	21.3	528	16.9
Jewish	4.3	2.9	3.3	5.9	5.4	132	4.2
French	1.7	1.3	1.5	1.0	1.8	54	1.7
Irish	16.5	14.0	12.1	14.1	10.8	419	13.4
English and Scotch	12.2	10.8	10.7	10.5	8.1	330	10.6
U. S. A.	27.2	29.4	25.4	19.5	20.1	764	24.5
All others	8.6	8.7	10.3	12.7	11.1	313	10.0

Similarly Table VI compares the nationality by percentages with the total figures of those nationalities included in the table.

TABLE VII. COMPARISON AS TO NATIONALITY OF LIVING, DEAD, AND TOTAL PATIENTS WITH CARCINOMA OF CERVIX

	BLACK		ITALIAN		IRISH		JEWISH		U. S. A.		TOTALS
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
Living	46	6.8	135	20.2	83	12.9	50	7.4	124	18.5	667
Dead											
1915-25	56	5.2	166	15.4	160	14.8	35	3.2	313	29.1	1,074
1926-37	123	9.0	227	16.6	176	12.8	47	3.4	327	23.9	1,365
Total											
1915-37	225	7.2	528	16.9	419	13.4	132	4.2	764	24.5	3,106

Table VII was compiled to study the significance of nationality as to prognosis. Italian and Jewish patients seemed to show an increase in percentages of living over dead patients for each of the 1915 to 1925 and 1926 to 1937 periods, and over the total dead of the corresponding nationality. Since the length of life with the disease is not stated, this does not prove that the prognosis is any better for the Jews and Italians than for any other nationality.

DISCUSSION

There must be some reason for the relatively low Jewish and high Italian incidence in carcinoma of the cervix. Several theoretical suggestions are of interest but no adequate explanation has been found. These suggestions are discussed as follows:

Sexual Activity and Multiparity.—Bagg³ has shown that "repeated forced breeding" in rodents tends to increase the incidence of breast and genital cancer. Knowing multiparity to be a constant factor in cancer of the cervix, it has never been shown that Jewesses were far behind Italian or Irish women in either fertility or multiparity. Questions on sexual activity asked of patients with carcinoma of the cervix failed to obtain cooperative or accurate answers.

Poverty.—Cancer of the cervix is found almost exclusively in the ward or clinic type of patient, rarely being seen in the type of patient who can afford private care. This suggests poor obstetric and post-partum care and neglect of symptoms of the lacerated and ulcerated cervix. One gets the impression in New York City that Jewesses are more liable to consult the clinics for symptoms of cervicitis than are the Italian or Irish women.

Circumcision.—Naturally the well-known rarity of cancer of the penis in circumcised men has led to the suggestion that this is in some way a factor in the

Here again the relatively high Italian and Scotch-English incidence, the constant Irish incidence, and the low Jewish incidence in carcinoma of the cervix is shown by the comparison.

TABLE IV B. COMPARISON BY PERCENTAGES OF NATIONALITY INCIDENCE IN THE SEVERAL TYPES OF GYNECOLOGIC LESION WITH THE TOTAL PERCENTAGES AVERAGE

	CERVIX	CORPUS A	OVARY B	VULVA C	BENIGN D	TOTAL AVERAGE	AVERAGE A B C D
Black	7.2	3.1	1.8	4.3	7.8	4.8	4.2
German	10.9	7.6	5.4	6.0	8.1	7.6	6.7
Italian	16.9	7.1	4.0	8.6	8.6	9.0	7.0
Jewish	4.2	19.6	21.6	7.8	35.5	17.7	21.1
Greek	0.3	0.0	0.0	0.0	1.4	0.8	0.3
Irish	13.4	18.6	3.1	15.6	15.8	13.3	13.2
Polish	1.0	0.4	0.0	0.8	3.0	1.3	1.0
Scotch and English	10.6	0.0	4.9	0.0	8.6	7.3	3.3
Austrian	3.3	2.6	7.2	4.3	3.2	4.1	4.3
U. S. A.	24.5	35.2	40.7	50.4	5.6	31.2	32.8
Others	6.7	5.6	5.4	1.7	1.0	4.0	3.4

This is a comparison of each individual lesion nationality incidence expressed in percentages and in total average percentages and total average noncervical lesion percentages. This substantiates the results of Table IV and IV A, except that when considered by percentage averages, negroes show a higher incidence of cervix cancer than of other gynecologic lesions.

TABLE V. COMPARISON BY FIVE-YEAR GROUPS OF NATIONALITY INCIDENCE

	1915-20		1921-25		1926-30		1931-35		1936-37	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Black	12	3.0	47	6.1	61	7.2	69	8.9	36	10.8
German	42	10.7	76	9.8	101	12.0	86	11.1	36	10.8
Italian	61	15.5	128	16.6	145	17.2	123	15.9	71	21.3
Jewish	17	4.3	23	2.9	28	3.3	46	5.9	18	5.4
French	7	1.7	10	1.3	13	1.5	8	1.0	6	1.8
Irish	65	16.5	108	14.0	102	12.1	109	14.1	35	10.5
English and Scotch	48	12.2	83	10.8	90	10.7	81	10.5	27	8.1
U. S. A.	107	27.2	226	29.4	214	25.4	151	19.5	67	20.1
All others	34	8.6	67	8.6	87	10.3	98	12.7	37	11.1
Total (3,106)	393		768		841		771		333	

It has been suggested that the incidence of carcinoma of the cervix in Jewesses is increasing. Various reasons are offered for this suggestion. These will be taken up later in the discussion of these statistics. Table V compares the incidence of various nationalities during five-year periods. Only the nationalities having the more prominent incidences are included so that the total in the table does not equal that shown in previous tables. It is notable that the incidence in Jewesses does not increase. Blacks do show some progressive increase in their incidence at Memorial Hospital and Italians do show some increase in the period 1936-1937, but no previous progressive incidence.

Probably twenty-year periods would present better evidence of increased incidence with succeeding generations. However, the available records do not permit statistical study previous to 1916.

DISCUSSION

DR. HERBERT E. SCHMITZ, CHICAGO, ILL.—Statistics, such as Dr. Smith has presented, must be interpreted very cautiously. At the County Hospital in Chicago, the percentage of Italians having carcinoma of the cervix is small and bears a direct relationship to the number of Italians admitted to the hospital. The highest incidence of carcinoma of the cervix occurs in the negroes, Poles, and Germans. These races also have the greatest number of admissions to the hospital. If statistics from different hospitals vary in this manner, other factors than nationality must play a role.

Practically all statistical analysis of this sort do, however, indicate that Jewesses, although they have no racial immunity to cancer, are less susceptible to cancer of the cervix. The factors which contribute to this lower incidence are not clearly understood. It has been suggested that the practice of circumcision among Jews is a factor, on the basis that the infected glans penis in the uncircumcised male may carry to the cervix the infection which by chronic irritation results in carcinoma.

Handley quotes an interesting observation concerning Fiji Islanders. In these Islands, there are 90,000 natives and 70,000 immigrated Indians. These races do not intermingle. The Fiji Islanders practice circumcision at puberty. The Indians do not. Hospital records in Snowa for a period of eight years, from 1925 to 1932, show only three cases of cancer of the cervix in Fijian women and 26 cases among Indian women. A similar study applied to our own population might throw some light on this subject.

Another factor, which it has been suggested may contribute to the lower incidence of cancer of the cervix among Jewish women, is the practice of Mosaic law, namely the cleansing after the forbidden period. This argument also is based on the premise that chronic infection and irritation are the forerunner of cancer of the cervix. Schiller, however, states that carcinoma of the cervix arises, grows, and develops before any signs of infection, erosion, or chronic irritation are demonstrable. In his opinion, chronic irritation is seldom a contributing factor to cancer of the cervix.

In this connection, some observations we made in 1932 on the influence of radium upon the bacterial flora of the female genitalia may be of interest. For some weeks or months following adequate x-ray treatment, bacteria disappeared completely from the vaginal discharge. After three to six months, there is a reappearance of the cervical and the vaginal flora. This reappearance of the cervical and the vaginal flora is often the forerunner of a recurrence of the malignant tumor. This does not necessarily indicate, of course, that the infection is a factor in the recurrence. However, I do think that Dr. Smith's suggestion that the vaginal flora in different races should be studied is a very pertinent one.

low incidence of cervix cancer in Jewesses. It was my impression that in the obstetric hospitals in New York City most male babies are circumcised before leaving the hospital, regardless of race or religion. Inquiry revealed that this is true of private patients but that less than 30 per cent of the male babies in the wards are circumcised before leaving. This included Jewish babies. It remains for someone to show whether the retained foreskin with its associated smegma bacilli is, or is not, a factor in cervical carcinoma.

Bacteriologic.—In an attempt to find a virulence index of vaginal organisms preoperatively, Ruge,⁴ Philips,⁵ and Clareberg⁶ studied the vaginal flora of normal women and of women with cancer of the cervix. In the cancer patients various types of streptococci increased and predominated with staphylococci to a lesser degree. However, they made no attempt to classify their patients according to race. I know of no comparative studies on the vaginal flora of noncancerous Jewesses and Italians, nor of patients with cancer of the cervix, as to racial differences in vaginal flora.

Hygiene.—A study of the laws of hygiene of Jewish people⁷ reveals the information that for seven days after menstruation a Jewess is considered unclean and is forbidden sexual intercourse. A cleansing bath and douche are advised before resuming sexual relations, but undoubtedly this is not peculiar to Jewesses. By questioning patients in the clinic at Memorial Hospital no marked difference has been detected in the chemical type of douches used by Jewesses and Italians. The suggestion that perhaps Jews as well as Gentiles of the present generation were not as orthodox in their religious behavior as their ancestors is not substantiated by any increase in cervical cancer incidence, as the result of any lapse of orthodox behavior.

Diet.—No marked difference has been detected between Italian and Jewish diets except in shell fish and the forbidden meats. Practically all other meats in New York City come from cattle slaughtered by the Kosher methods; meat for Jews differing only in that it is slaughtered by a special agent having the necessary religious qualifications. It is doubtful if this could play any part in the difference in cancer incidence.

Inbreeding.—Experimental laboratories are well aware that certain strains of rodents are "tumor resistant" while other strains are "tumor susceptible." Some strains are resistant to some types of tumors and susceptible to other types. These qualities can be maintained by inbreeding, thus maintaining a pure strain. Cross breeding lessens the resistance. The well-known reluctance of Jews to marry out of their own race may have some significance in their maintaining a low incidence of cancer of the cervix. Certainly Jewesses are not resistant to other types of genital and breast cancer.

CONCLUSIONS

1. In carcinoma of the cervix the relatively low Jewish incidence and high Italian and Scotch-English incidence is established in contrast with the nationality incidence of the remainder of the Gynecological Clinic at Memorial Hospital.

2. Various theories for this incidence have been discussed but no adequate explanation has been found.

3. The most plausible explanations deal with circumcision and other racial customs.

4. Further studies on the racial differences in vaginal flora are suggested.

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the pure breast proteins by blood and other tissue proteins was avoided. These we felt might produce nonspecific reactions as in the case of the placental extracts.

Accordingly, it was decided to use colostrum in various dilutions intradermally on pregnant and nonpregnant women to determine if they reacted alike or differently under these conditions. We were rather surprised to find that pregnant women gave a faint response or no reaction to the injections and nonpregnant individuals reacted rather vigorously. These results seemed to be quite constant. As the number of patients injected increased, the high percentage of correct diagnosis made by the test became quite significant.

PREPARATION OF MATERIAL

Colostrum from primiparous pregnant women is expressed from the breast manually into a sterile glass container after cleansing the nipple and areola with ether. It was found that the colostrum was most easily obtained at about the twenty-eighth week of pregnancy. It was then diluted with equal amounts of sterile normal saline solution. To 10 c.c. of this mixture 1/10 c.c. of 1 to 100 merthiolate solution was added as a preservative, and it was kept in the icebox.

TECHNIQUE OF INJECTION

The flexor surface of the forearm of the patient is sponged lightly with a piece of cotton saturated with ether. A weal is formed by injecting exactly 1/50 of a c.c. of the diluted colostrum intradermally, using a tuberculin syringe and a 26 gauge needle for the purpose. A second syringe and needle are used to make a similar-sized weal with physiologic salt solution a few inches lower on the arm. This is to be observed as a control. The reaction is noted at ten minutes, one-half hour, and one hour. Readings made at the half hour are usually sufficiently marked to indicate whether the test is positive or negative.

If the patient is pregnant, the weal produced by the injection of colostrum will appear pearly, resembling a fresh mosquito bite with little or no pinkish areola surrounding it. The site of injection will scarcely be recognizable in an hour, except for the needle prick in the center. The control produces no reaction beyond the raised area caused by the injection.

When the patient is not pregnant, a marked difference in the reaction is seen. The weal tends to remain raised and pearly until a few minutes after injection when it begins to increase in diameter, eventually becoming two to three times the size originally produced by the injection, without changing in color. There then appears an areola of pink to red one to two inches in diameter which is irregular in contour, color, and depth and projects lymphangitic pseudopodiums from its periphery. The reaction steadily grows in intensity for an hour and persists for four or five hours. The control injection with physiologic salt solution in these patients gives neither increase in the weal or areola pigmentation.

RESULTS

Our report deals with the injection of 265 known pregnant women in various stages of pregnancy and includes toxic as well as nontoxic cases.

The controls comprise 358 known nonpregnant cases of which 100 were adult males, 45 were children below the age of fifteen, 50 menstruating women, 50 postpartum cases, and 113 cases of either normal nonpregnant women or women with various known gynecologic conditions, carcinoma, fibroids, ovarian cysts, etc. Finally 50 unknown problem cases were tested to establish the diagnosis.

Of the 265 pregnant women described as known to be pregnant, in approximately 50 cases the test was applied before the fourth month, although the signs and

A SKIN TEST FOR THE DIAGNOSIS OF PREGNANCY*

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THE use of skin reactions as an aid in clinical diagnosis of many conditions has long been recognized as a valuable procedure. The Von Pirquet, Schick, Dick reactions and the use of various proteins intradermally for the purpose of detecting allergic sensitivity have all proved their clinical usefulness. There are so many biologic differences between pregnant and nonpregnant individuals that the possibility of being able to differentiate between these groups by means of a skin reaction to some antigen seemed not too remote.

Falls and Bartlett,¹ in 1914, attempted to extract a protein from the placenta which might be used for this purpose. The results were unsatisfactory, due to the fact that the methods employed were not sufficiently refined to yield a pure protein as was hoped, but a mixture of proteins was obtained which led to nonspecific reactions. By using better methods of extraction and preparation of the placental proteins, Cohen and Freda² attempted to produce precipitin reactions and specific skin reactions that might be useful diagnostically. When the precipitin reaction was tried, serum of known pregnant women reacted positively in about 75 per cent of the cases. The serum of males and normal females did not react. Certain nonpregnant women with gynecologic pathology gave a rather high percentage of false positive reactions which nullified the usefulness of this method for practical diagnostic purposes.

The use of placental tissue extracts in producing skin reactions was to some extent successful, since about 75 per cent of the patients tested by intradermal injections gave positive reactions if pregnancy existed and negative if no pregnancy were present. This result was in accord with the results reported by Esch,³ Englehorn and Wintz,⁴ Gruskin⁵ and Schwartz⁶ who made similar tests have reported a higher percentage of correct diagnosis.

The high percentage of false reactions (25 per cent) rendered the use of these procedures for diagnostic purposes useless, and so it was decided to try to find an antigen that would give more specific reactions.

The possibility of using proteins extracted from breast tissue was suggested, since it was thought that during pregnancy the cells of the breast might secrete a protein of somewhat different composition than other body proteins. On further consideration this idea was rejected in favor of using colostrum which must contain the proteins produced by the breast in early pregnancy. By using this material the contamination of

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symptoms were sufficiently marked to lead us to make a clinical diagnosis of probable pregnancy later confirmed. The rest of the 265 women had sufficiently advanced in pregnancy to give positive signs of pregnancy. In this group there were 5 false reactions. In 2 women nonpregnancy reactions were obtained and the patients later were shown to have a living fetus in the uterus. One of these later gave a positive pregnancy reaction, and the other failed to return for retest.

There were 3 cases in which a weak reaction indicated nonpregnancy. However, this reaction persisted for only forty-five minutes and had disappeared by the end of the hour contrary to the reaction seen in nonpregnancy. Early in pregnancy and toward the end of pregnancy a slight reddening around the vesicle produced by the injection might be termed a weak or false nonpregnancy reaction. It differs from the true nonpregnancy reaction in the width of the areola, the depth of color, and the fact the weal does not enlarge after injection. It differs from pregnancy reaction in that there is some color around the weal. A similar reaction has been seen in the early puerperium. A group of 15 patients were tested during labor, and it was seen that the stage of labor made no appreciable difference in the reaction which was similar to the weak nonpregnancy reaction just described.

One hundred and thirteen known nonpregnant females were tested. Forty-five of these were out-patient gynecologic cases and 68 were patients in the gynecologic wards, mostly postoperative cases at Cook County Hospital. Typical nonpregnancy reactions were obtained in all but 4 cases in which a typical pregnancy reaction was obtained, which would have led to an incorrect diagnosis if the test alone had been relied upon.

On further study of these false reactions, the 4 women who gave this reaction were all in the menopause, not having menstruated for from five to seventeen years. Three of these cases were advanced Group III carcinomas of the cervix uteri, and the fourth was a simple precidentia seventeen years after the last menstrual period.

Fifty menstruating women were studied; all of these gave nonpregnancy reactions. Five cases were studied throughout the menstrual period.

A group of 45 children of both sexes were studied, varying in age from 2 to 15 years. A reaction similar to that seen in pregnancy was obtained in all cases up to the age of about 10 years, at which time modified nonpregnant reactions were seen in both males and females.

One hundred male patients of varying ages from the medical service of the Cook County Hospital were studied. These were routine medical service patients with cardiac disease, hypertension, blood dyscrasia, etc., as is customarily found in a medical ward. None of these gave positive pregnancy reactions. Three of them gave modified nonpregnancy reactions; one was a boy of 15 and the others were elderly men, 65 and 75 years of age.

There were 50 post-partum cases varying from two to eight weeks postdelivery. In all but 3 of these the reaction was that of nonpregnancy. This was noted whether or not the patient was nursing her baby. The 3 pregnancy reactions were all in women eight weeks post partum, one was menstruating, the other two admitted exposure, but sufficient time had not elapsed to determine whether or not pregnancy existed. In the puerperium therefore it would seem that the test was correct in 96 per cent of the cases. Obviously the test would rarely be applied in such cases for the practical purpose of diagnosis.

DISCUSSION

The interpretation of the reaction is not so simple. From a consideration of the foregoing results, it appears that nonpregnant individuals have become sensitized to a specific protein contained in colostrum from primiparous women. This protein probably is not contained in human milk or in colostrum or milk obtained from the cow, since injections made using these substances as controls gave no specific reactions comparable to those obtained with human colostrum. If it is present, the specific reaction is masked by other substances in these biologic materials. Human milk taken as soon as the breasts began to secrete milk (three to four days after delivery) and used

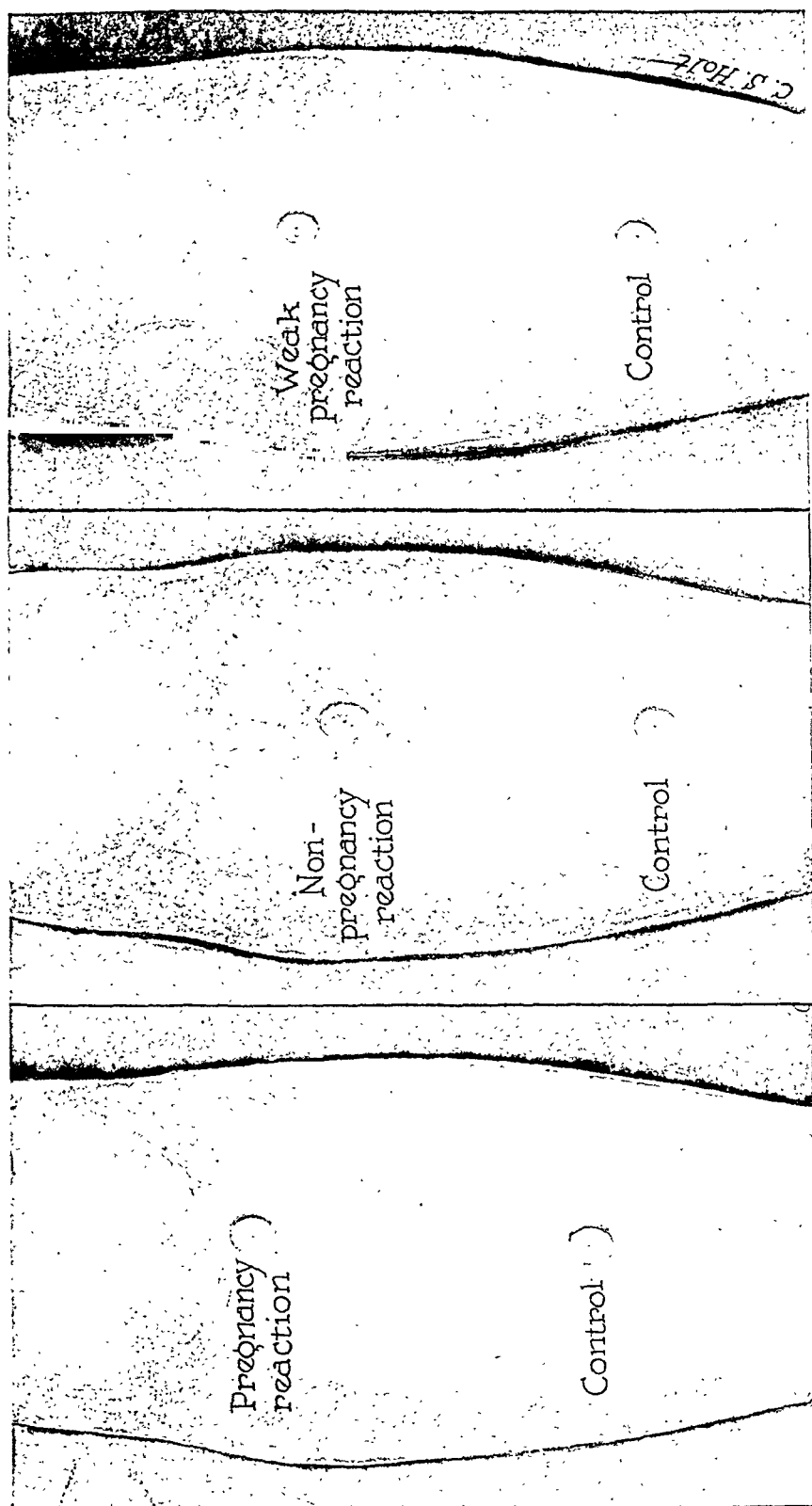


Fig. 1.

The reaction of the males to injected colostrum suggests that the male breast secretes sufficient of the specific solution over a period of years to sensitize but not immunize the patient. On the whole the reactions obtained in males have been of less intensity than those seen in nonpregnant females. This may be due in part to differences in the skin texture.

Older patients, both male and female, gave a reaction of diminished intensity which decreased progressively with the increase of age. This may be explained by the assumption that breast activity gradually decreases, finally ending sensitization. We realize that the explanation of these results is far from complete at this time and further work is in progress to attempt to prove or disprove some of our ideas.

Two patients with ectopic pregnancy, one with an unruptured isthmie pregnancy (six weeks) and one with an aborting ampullary pregnancy (ten weeks), gave pregnancy reactions, the correctness of which were confirmed by operation.

The most interesting group were the problem patients in whom the test was applied to try to make the diagnosis of early pregnancy one to three weeks after missing the first period. The difficulty here is the fact that very early pregnancies theoretically may be present, produce a reaction, terminate by death and expulsion of the fetus without producing sufficient clinical evidence to prove or disprove the presence of pregnancy. In a few cases we have been able to hospitalize the patient and make sure of the diagnosis, in others we have had to depend on clinical observation which we realize is open to some objection. In spite of this, we have been able to make the correct diagnosis in 46 cases in which sufficient time has elapsed to prove or disprove the correctness of the diagnosis as measured by the test.

It is important to note that considerable familiarity with the test is necessary for the correct interpretation of the reactions produced. After doing about 25 tests in pregnant and nonpregnant individuals, the interpretation of these reactions is quite simple. This is in accordance with the experience of others who use intradermal injections of antigens for diagnostic purposes. From our present experience, we are sanguine regarding the diagnostic value of the test. If our results are confirmed by others, it will make the diagnosis of early pregnancy much simpler, quicker, and more economical than the methods we now have at our command.

CONCLUSIONS

1. An intradermal injection of a colostrum solution gave no reaction in 98 per cent of pregnant women.
2. Nonpregnant women reacted to similar injections with the formation of a characteristic weal and areola in 96 per cent of cases.
3. Males reacted similarly to nonpregnant females.
4. Children before puberty reacted similarly to pregnant women.
5. The test seems to have value as an aid in the clinical diagnosis of pregnancy.

We wish to acknowledge the assistance and cooperation of Professor William H. Welker of the Department of Physiological Chemistry in the preparation of the antigens and his part as consultant in the pursuit of this research.

for injection failed to give a specific reaction. The colostrum of multiparous women frequently gave a slight nonspecific reaction in both pregnant and nonpregnant individuals. Attempts to extract the active principle of colostrum obtained from primiparas, which is responsible for these reactions, using oil, ether, alcohol, ammonium sulphate for extraction, or dialyzing through parchment membrane, resulted in failure. It would seem that dilution by milk, alteration of the breast function by previous pregnancy, and attempts at purification by chemical methods, all alter the substance responsible for the test in a manner which prevents the characteristic response on injection.

Various dilutions of colostrum were tried and different amounts were used. When undiluted colostrum was injected the reaction was more marked, and some of the pregnant women showed a weal and areola approaching that seen in nonpregnant women. When more than one-fiftieth of a cubic centimeter was used similar side reactions were obtained. This is in line with the experience of the men working in the field of allergy (T. Nelson⁷).

To determine whether a nonspecific protein other than milk proteins would give these reactions, gelatin was used as a control in some cases. No reactions were obtained in the amounts used. Further work is in progress in an attempt to obtain the active substance in pure form.

The failure of the pregnant woman to react to the injection we feel is best explained by the assumption that early in pregnancy the production and absorption of the active substance from the breast leads to an immune state which prevents the local reaction at the site of injection, except the weak reaction seen in about 80 per cent of the cases in the first six and the last three weeks of pregnancy, during labor, and in the early days of the puerperium. The weak reactions seen at this time are difficult to explain. It is possible that toward the end of pregnancy the breast may cease producing the specific substance responsible for the reaction. The weak reactions begin to appear about two weeks from term and the typical nonpregnant reaction begins to appear about the twelfth to fourteenth day of the puerperium. Naturally the test will not be applied clinically at the end of pregnancy or during the puerperium so that the weak reactions seen at these times are of only academic interest.

As a matter of interest 5 menstruating women were injected daily throughout their periods, to determine what effect if any this would have on the reaction. These patients react as nonpregnant women the first day of the period, and the reaction gradually decreases on the following days. They react as pregnant women on the last day. The reaction gradually returns to the nonpregnant type after three or four days. This is significant because of the false conclusions that might be drawn from tests performed at this time of the month. It is not clear what influences this change unless the breast stimulation produced by the menstrual cycle at this point leads to absorption from the breast of sufficient amounts of colostrum to produce a temporary immune reaction.

The negative reactions seen in children before puberty would suggest that they have not yet produced and absorbed enough of this protein to become sensitized to the colostrum injections.

nancy. We operated and found an old hematosalpinx. The fetus had been dead for some time. The reaction was negative for pregnancy in spite of the fact that the hematoma in the tube probably had been produced by an ectopic pregnancy.

If this test does prove its merit, it is obvious how valuable a test that can be read in an hour and at the expense of a little salt solution and colostrum will be as an addition to our diagnostic armamentarium.

OBJECTIONS TO INDUCTION OF LABOR IN NORMAL PREGNANT WOMEN*

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THIS discussion is limited to the induction of labor in the normal pregnant woman, the woman who has no toxemia, no disproportion, no disease. In the past ten years advice to induce labor on the mildest indications is increasing rapidly in the literature. Convenience of the patient, wishes of the patient or her family, convenience of the physician, living a distance from the hospital, desire to have the delivery occur in "working hours," have all been brought forward as indications for the induction of labor. I doubt not but that many of our noted obstetricians long since dead, must be clamoring to rise again and take issue with this type of "streamlined" obstetrics.

May I call your attention to the dangers, physical and legal, which are always present when one interferes with the normal processes of pregnancy and labor.

Many authors state that the size of the baby indicates whether or not the patient is at term or over-term. From my own experience and from observation, I know that experienced physicians miss the weight of babies before birth as much as two pounds. In the series of patients included here, there are two who went over-term as we usually compute the term from the menstrual period. One patient was thirty-three days over and her baby weighed 3,295 Gm. The other was thirty-two days past term and the baby weighed 4,250 Gm. This is quite a difference in weight.

The x-ray film can give an idea of the size of the baby, but even with that aid, experienced physicians many times miss the weight by pounds. A well-known obstetrician of my acquaintance insisted upon a cesarean section upon a patient who he said had a very large baby. The baby weighed under 6 pounds. Polyhydramnios caused the large uterus.

Some couples whose eugenic history is such, naturally have large babies. This is seen frequently in patients who deliver ahead of schedule. Two patients in this series delivered 4,400 Gm. babies one week before expected term and another ten days after the expected term. The largest baby, which weighed 4,515 Gm., was delivered twenty-three days past the expected term. On the other hand, I have seen babies who weigh from 5 to 6 pounds present all the signs of prematurity. Koff and

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I am indebted to Dr. Paul W. Sweet for securing the statistics for this paper.

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DISCUSSION

DR. LAWRENCE M. RANDALL, ROCHESTER, MINN.—We now have two accepted tests for pregnancy with an accuracy proved to be more than 98 per cent from long experience, the Friedman and the Aschheim-Zondek. One must compare any new test to this standard regardless of the time factor involved in the two tests mentioned.

A large number of so-called tests for pregnancy have appeared in the past twelve years; their average incidence of error may very reasonably be put at 20 per cent. Perhaps a smaller incidence of error will occur in the hands of one who is expert in the taking of histories and their interpretation and who is expert in physical examination. One who is less expert in such matters and who relies upon a relatively inaccurate laboratory test may actually increase his percentage of errors.

A certain number of errors will always occur with any "pregnancy test." These tests are for the detection of substances present in bodily fluids or secretions that are most commonly associated with the presence of pregnancy but which may be found in association with other conditions.

Skin tests, based on the intradermal injections of protein substances, depend upon allergic reactions and are therefore subject to the errors common to such tests. Allergic individuals who are sensitive to many foreign proteins may give a reaction that is false as far as pregnancy is concerned. The ovaries of the non-pregnant rabbit and the immature mouse are much more specifically sensitive than is the skin. One must be familiar with wheal formation to minimize the personal error of interpretation. An error of 10 per cent is probably to be expected from this source, with the placental extract used in the method of Gruskin.

However, much as one may distrust skin tests as a whole, we cannot help but be impressed with the results that Dr. Falls and his co-workers have obtained with a simple and logical experiment. They have presented a very thorough piece of work and conservatively asked for further trial by themselves and others.

DR. A. J. RONGY, NEW YORK, N. Y.—The test described by Dr. Falls is an important addition to the already established pregnancy tests. It may help to solve the diagnosis in early unruptured ectopic pregnancy. Last week, one of my associates was confronted with the difficulty of diagnosing an unruptured ectopic pregnancy in a young woman. The ordinary Aschheim-Zondek test on a rabbit and a mouse proved to be negative. The pathologist then made a definite diagnosis of pregnancy upon sectioning the ovary of the mouse, basing it on microscopic changes in the cells of the ovary. The patient was operated upon and was found to have an early unruptured tubal pregnancy.

DR. FALLS (closing).—I appreciate the fact that when considering skin reactions there is no test which gives 100 per cent of correct readings. The Wassermann test has its limitations, as do the Widal and all of the allergy tests. Yet in spite of these limitations these tests have stood the test of time and are useful clinically. We hope that our test will also stand the test of time which will determine its value.

One must do a number of these tests to become familiar with the reaction before beginning to depend upon them to make a clinical diagnosis. We feel that the interpretation after about 25 tests should familiarize one with the reaction sufficiently to make his judgment correct.

The paper reports the diagnosis of two unruptured ectopic pregnancies proved by operation. The other day we had a case in which we suspected an ectopic preg-

after birth, the organism found in the child was also present in the infant. The maternal morbidity was nearly 50 per cent in the 46 cases reported.

While it is true that many writers report that their morbidity rates are not higher in induced cases, I know by experience that interference in any manner which involves vaginal manipulations raises my morbidity rate in spite of anything I may do about the technique in the delivery rooms. I am sure the same bacteria are lurking around delivery rooms all over the country. Perhaps the thermometers vary so the readings are not so high or the patient's temperature is taken less frequently. Whatever it is that is different, I cannot bring my morbidity rates down to the same level as the rates among the patients who deliver spontaneously.

Post-partum hemorrhage is increased in induction cases and is mentioned in many articles in the literature. While it is true that hemorrhage is more frequent in pathologic cases, it cannot be overlooked as a source of trouble in normal women.

The use of oxytocic drugs always carries a very definite hazard. I need not stress to this Society the fact that rupture of the uterus, extensive lacerations of the cervix, and brain hemorrhage are common sequelae. The use of quinine in large doses is said to have a bad effect on the ears of the fetus. I have seen 3 to 5 gr. doses of quinine produce terrific contractions of the uterus. One multipara in my practice delivered in thirty minutes following a 5 gr. dose of quinine. Her cries of pain could be heard throughout the hospital.

From the legal standpoint, I believe we are courting trouble if some patient should be inclined to take issue with us after delivery, especially if the baby should be injured or die. W. C. Woodward is quoted by DeLee as follows:

No professional standard anywhere at any time could justify a physician in doing anything that would jeopardize the life and well-being of mother or infant solely for the physician's convenience. Moreover, consent by the father or mother, even with a thorough understanding of the matter, would not excuse a physician who deliberately expedites labor solely for his own convenience, to the material danger of mother and child.

It may be questioned whether a physician can lawfully do anything to expedite the onset of labor unless it is necessary to do so for the life of mother and baby—A child might have a right of action against the physician who is responsible for the injury—notwithstanding anything the parents may have authorized to be done in conduct of labor.

There have been many indications for induction of labor in normal pregnant women. Slemons, in 1932, gave nervousness in woman past term, previous precipitate labor, and living a distance from the hospital as indications in some 35 to 50 cases. Other authors have mentioned convenience of the patient and the doctor, solicitation by relatives, and many other flimsy reasons. We might as well say that we should do cesarean sections on all these patients, using the same indications.

My observations of patients delivered by obstetricians in my own city who induce labor is that in many cases the cervix and the vagina are badly torn and scarred. The history in most of these normal patients is

Potter say, "unfortunately there is no reliable sign or collection of signs by which antenatal diagnosis of abnormal size of the fetus can be definitely established except perhaps in extreme cases." To this I agree. In my opinion, therefore, we cannot safely predict that a patient is at term, or past term, by the size of the baby.

Most of us put considerable reliance on the date of the last menstrual period in predicting the time of delivery. We know that periods may be very irregular. We are beginning to realize that ovulation is also irregular as to time. Such being the case, it is conceivable that a patient could have had a delayed ovulation or period at the time she became pregnant. Again there are those who menstruate only four to six times a year. I recall years ago having a patient who delivered a baby weighing less than 6 pounds exactly one year after her last period. Surely we could not classify that pregnancy as postmature. If we accept the term of pregnancy as 273 days and ovulation as necessary before pregnancy, then a patient who ovulates just previous to a period should arrive at term later than a woman who ovulates in the middle area of the intermenstrual period.

The date of the period, therefore, is not an accurate guide.

We have tried to gauge term from the date of quickening. Several years ago I made a detailed study of this point on 750 cases from private practice. The women were intelligent and cooperative. They were as accurate as one could expect. The menstrual and life dates were known. A student of higher mathematics was given the job of working out a formula, and when we were all through, no accurate formula could be deduced. The error was as great for the life date as for the menstrual date.

The life date, therefore, cannot be used as an accurate guide.

What are the common complications of induction which are not usually seen in spontaneous labor? The outstanding one is prolapse of the cord. Practically without exception all writers mention it. The report of the Central Association of Obstetricians and Gynecologists shows that prolapse of the cord is three times more frequent in 1,669 induced cases. Plass reports a rate of nearly 1 per cent.

With few exceptions the fetal mortality seems to be higher in induced cases. In my personal experience this is true, because early in my practice I induced labor more frequently. It is much more difficult to explain the death of a baby to the distressed parents when labor has been induced. One should not forget that it is better to have a live baby past term than a dead one at or before term.

Placental infection is reported to be much greater in induced labor. Penfold and Butter report 61 per cent of the placentas of induced cases were infected, against 24 per cent in spontaneous cases of labor. They state that the longer the postinduction period the greater the possibility of placental infection. Mixed infection of the placenta holds greater danger for the child than single infection. In 15 of the 46 cases of induced labor with infected placentas, the child died. In seven stillbirth cases only two had no infection in the placentas or fetus. In five deaths

4. Twenty-five babies weighed 4,000 Gm. or more, about equally divided in the following groups:

5. The delivery dates being known and the expected term dates being computed, the 200 patients were divided into four groups: (A) Those who delivered in the interim between seven days before term and the expected term; (B) those who delivered one to seven days past the expected term; (C) those who delivered 8.15 days after expected term; (D) those who delivered sixteen days or more after expected term.

TABLE III

AGE	PARA	WEIGHT GM.	LABOR			NO. DAYS +	REMARKS
			1ST STAGE	2ND STAGE	3RD STAGE		
32	iv	3,510	1:45	7	7	16	
35	ii	3,295	15:30	83	7	33	Forceps
28	ii	3,444	5:35	9	5	20	Forceps
31	ii	3,770	7:15	15	5	16	
25	i	3,487	20	207	11	26	Forceps
41	iii	4,360	10:50	15	4	17	
25	i	3,665	12:25	57	6	17	
20	i	3,595	21:30	48	16	28	Forceps
28	i	3,670	Too rapid			16	Forceps
22	i	4,155	19:25	77	4	25	Forceps
32	iv	3,146	1:15	24	8	22	
28	ii	4,085	2	46	9	20	
24	i	4,515	27:10	1:10	6	23	Forceps
26	iii	3,900	2:30	25	8	18	
40	ii	4,165	12	44	6	18	Forceps
19	i	3,445	13	34	4	27	Forceps
33	iv	4,290	4	20	11	28	Forceps
22	i	3,740	13:30	55	5	16	Forceps
35	iii	3,060	2:15	12	13	18	
28	v	4,250	1:40	18	2	32	
28	ii	3,530	10	50	6	21	Forceps
Total 21							

The results are summarized in Tables I, II, and III. For those who may be interested, Group D is given in detail. The number of babies weighing over 4,000 Gm. average about the same in Groups A and B, at about 10 per cent. In Group C the percentage is raised to 15 per cent and in Group D to 33 per cent. It is true, therefore, that babies carried past the expected term are larger. Most of the babies weighed from 3,000 to 4,000 Gm. (151). There were 5 babies who weighed less than 2,500 Gm. Only one baby weighed more than 4,500 Gm., a percentage of 0.5 which compares with Koff and Potter's findings of 19½ per cent in 20,219 deliveries at the Chicago Lying-in Hospital.

6. As you can see by the table, there is a wide variation in the weights of babies delivered by normal women. The most marked difference was in the group of patients who delivered from seven days before term to term. Here the smallest baby weighed 1,814 Gm. and the largest 4,400 Gm., and no mistake was made in the reckoning by the patient or the physician. The pediatricians who examined the large babies hesitated to say definitely that any of them were postmature.

There was no fetal or maternal mortality in this series, and, so far as I know, all the babies are alive and well at this time.

The number of forceps deliveries is high since nearly all of these patients were delivered under analgesia and were not cooperative in the second stage of labor.

From observation and a review of this series, I firmly believe we are not justified in interfering with the natural processes of pregnancy and labor in normal women. I protest against such a procedure.

that of a tedious attempt to put the patient into labor by means of medicine, bag, rupture of the membranes, bougies, or a combination of two or more. In many the cervix did not dilate and Dührssen's incisions were made. In others pituitrin or thymophysin was used and the cervix torn as a result of the strong uterine contractions.

Many authors mention certain conditions which should be present before an attempt is made to induce labor. F. J. Iiams lists them as follows: (1) Patient under observation for months, (2) patient's health perfect, (3) past history good, (4) no disproportion or malposition, (5) pregnancy advanced to eight and one-half months, (6) baby must weigh 6 pounds or more, (7) cervix must be soft, effaced or partially dilated.

It is easy to determine the first four conditions, but the last three are open to marked variations in interpretation. Iiams mentions that his smallest babies weighed 5 pounds 2.5 ounces and 5.5 pounds. How many more weighed less than 6 pounds is not recorded.

For the purpose of this article a series of 200 consecutive normal pregnant women were studied. Data were secured similar to that used by other authors in an effort to influence the medical profession to interfere with pregnancy at or near term. All patients who presented signs of toxemia or any of the accidents of labor were eliminated. What do we find?

1. The average age of all was 28.6 at delivery.
2. There were 91 primiparas and 109 multiparas.
3. The average weight of all babies was 3,507 Gm. The largest weighed 4,515 Gm. and the smallest 1,814 Gm.

TABLE I. WEIGHT OF BABIES

DAYS BEFORE OR AFTER TERM	LESS THAN 2,500 GM.	2,501-3,000 GM.	3,001-3,500 GM.	3,501-4,000 GM.	4,001-4,300 GM.	4,301-4,515 GM.
-7 to 0	3	8	28	20	4	2
1 to 7	2	9*	35	22	6	
8 to 15		3	15	17	5	1
16+			6	8	5	2
Total	5	20	84	67	20	5

*One set twins.

TABLE II

DAYS + OR - TERM	AVERAGE AGE	PARITY				AVERAGE WEIGHT, BABY, GM.	NO. BABIES WEIGH- ING 4,000+ GM.	AVERAGE LENGTH LABOR			NO. FORCEPS DELIVERIES	WEIGHT OF LARGEST BABY, GM.	WEIGHT OF SMALL- EST BABY, GM.
		I	II	III	IV+			1ST STAGE HR.	2ND STAGE HR.	3RD STAGE HR.			
-7 to 0	28.4	30	24	6	5	3,347.4	6	11.15	42+	7.9	26	4,400	1,814
1 to 7+	28.8	32	22	13	6	3,356.8	6	9.57	41.5	7.4	38	4,200	2,325
8 to 15+	28.6	21	11	8	1	3,565.5	6	12.52	44.8	6.8	20	4,400	2,675
16+	28.7	8	6	3	4	3,765.5	7	9.41	43.5	6.8	12	4,515	3,060
Grand average or total	28.6	91	63	30	16	3,507	25	10.54	42.9	7.2	96	4,378	2,468

convinced that if there is any evidence that justifies the assurance that a patient is due or near term it is the preparation of the lower uterine segment and cervix. Most often labors are longer and more complicated where these signs are not present. Premature labor from whatever may have been the cause with inductions, especially in primipara, are too often long, tedious, and difficult. These observations cause us to reason that if the lower uterine segment and cervix are prepared for labor, an induction is contraindicated other than for definite reasons; also if the lower uterine segment and cervical preparation is not present, the hazards are too great to warrant interference.

May I suggest these observations for your serious consideration since, if this reasoning is true, there can be no reason for the induction of labor other than for definite indications.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—As Editor of your official source of publication I sometimes have a feeling of doubt and hesitancy about having included in our pages so many papers dealing with routine induction of labor. We try to be catholic, but I feel a hesitancy in accepting papers of that type, especially when we have reports of series of several hundred cases in routine obstetric practice where labor has been induced, often without any regard to the condition of the cervix.

I do not agree with Dr. Cornell as to all of his restrictions, because some women require an induction of labor who are only a little bit removed from the normal. But in consenting to do that you must have certain conditions present, of which the principal one is a normally prepared cervix.

DR. ALBERT W. HOLMAN, PORTLAND, ORE.—In 1936 my late Associate, Dr. Mathieu, gave our results in 750 inductions of labor. At that time he spoke of our induction routine, and I think a great many men misunderstood him and thought he said routine induction. Our inductions are not routine. I am making no plea for routine induction of labor but would like to give a few of our results in our series which now amounts to 1,163 cases. Our corrected fetal mortality is 0.7 of 1 per cent; our maternal mortality is 0.3 of 1 per cent. We have had one case of prolapsed cord and no case of separation of the placenta in this series.

I would like to ask Dr. Cornell what type of induction he does. The type that Mathieu advocated was medicinal induction of labor, and he always stressed the point that the membranes should never be ruptured until the cervix was effaced.

DR. H. B. VAN WYCK, TORONTO, CANADA.—Do not all the considerations that Dr. Cornell has brought forward to contraindicate induction of labor in normal cases apply equally well to the effort that is made to escape borderline disproportions by premature induction of labor?

DR. A. J. RONGY, NEW YORK, N. Y.—Modern contraceptive methods and the practice of birth control have thrown a new light on the traditional term, "overdue," in the practice of obstetrics. A great many intelligent women now know exactly when impregnation may have taken place. The last date of menstruation is no longer a true criterion upon which the duration of pregnancy can be predicted properly. I have a series of patients whose calculation for the possible onset of labor were more correct than mine, because they knew actually when pregnancy might have ensued. Their date for labor was usually ten to fourteen days later than the established obstetric calculations would indicate. Therefore, in many cases the onset of labor is delayed, not because the woman is actually "overdue," but because pregnancy took place approximately close to the menstrual period.

I have never induced labor for the convenience of the patient or myself. That is definitely meddling obstetrics. The expert obstetrician may at times induce labor at an appointed time and not run into any untoward complications, but should this method become a recognized obstetric procedure, it would cause the death of many mothers and babies. The only indication for induction of labor is when the pregnancy becomes dangerous to the mother and rarely when the child becomes oversized. However, the weight of the patient must be carefully watched in all

DISCUSSION

DR. JOHN H. MOORE, GRAND FORKS, N. D. (By Invitation).—Dr. Cornell has pointed out that we have no accurate criteria by which we can determine the weight of the baby in utero or the presence of postmaturity. To that might be added that we do not know what institutes the mechanism of labor. When we attempt to induce labor by medical or mechanical means, we are attempting to set in motion a force whose effectiveness is not predictable with any degree of accuracy. Two cases illustrate the problem:

CASE 1.—A multiparous patient, gravida v, para iii, entered the hospital on May 9, 1940. Her estimated date of confinement was May 14. She was not in labor and came to the hospital solely because of a feeling that labor was imminent. Her condition was entirely normal, and upon rectal examination, the cervix was found to be completely effaced, the os dilated to 4 cm. and the head engaged in occipitoanterior position. I ordered one ounce of castor oil, to be followed one hour later by a tap water enema and three minims of pitocin by hypodermic injection. Forty-eight minutes after the pitocin had been given she delivered a baby boy weighing 3,960 Gm. During the third stage, which lasted eight minutes, she lost 400 c.c. of blood, due to the fact that the placenta separated but became constricted by the contracted cervix. Following the removal of the placenta, she had an additional blood loss of 500 c.c., making a total blood loss of 900 c.c. This patient illustrates the unusual violence which may characterize the onset and course of a labor which has been induced by the most common medical measures.

CASE 2.—In contrast is the case of another multiparous patient, a gravida ii, para i, upon whom I also induced labor for convenience. Her previous labor, conducted elsewhere, had lasted forty-eight hours and was terminated by a forceps delivery. Her estimated date of confinement was July 17, 1940, and she entered the hospital on July 19, 1940. Her pregnancy also had been entirely normal and she was in excellent condition. The cervix was soft, one half effaced, the os was dilated to 2.5 cm., and the head was engaged in occipito anterior position. Induction of labor was attempted with castor oil, enema and pitocin. Twenty-four hours later, these measures having failed, the membranes were ruptured artificially with the resulting discharge of a large amount of liquor amnii. *Nine days later* labor began and, after a first stage of fifteen hours and a second stage of fifty-two minutes, the patient delivered a normal baby girl weighing 4,680 Gm. The blood lost was 30 c.c., and there were no puerperal complications.

Here are two cases of induced labor in normal pregnant women at term, induced, theoretically, for the patients' convenience. The violent onset of labor in one, with the complication of postpartum hemorrhage, and the latent period of nine days in the other, with the membranes ruptured, made me wish that I had not induced either.

I will admit that one may review large series of cases where labor has been induced on normal pregnant women, with no apparent complications in either the mothers or their babies; but if pregnancy and labor are still to be regarded as normal physiologic processes, the burden of proof for the safety, the efficiency, and the wisdom of the induction of labor in normal pregnant women is directly the responsibility of the obstetrician who presumes to interfere with these natural processes. As I get older, I find myself less willing to assume that responsibility, even though many of my patients live in towns without hospital facilities and often in communities where medical attendants are not readily available. When I do assume that responsibility, as in the cases mentioned, I feel that I have let expediency overrule obstetric judgment.

DR BUFORD G. HAMILTON, KANSAS CITY, Mo.—Dr. Henry Schwarz and those outstanding leaders of his time always taught and practiced that if women were left alone they could and would have their babies. They also advocated that the membranes were for the protection of both the mother and child. Sad experience has taught me how wise these fundamentals are today.

The changes in the lower uterine segment and cervix are important to note in the last weeks of pregnancy. As I have watched these phenomena, I am

cuss all of these unusual tumors but rather to confine my discussion to the so-called granulosa cell tumors of the ovary and report two cases of precocious puberty.

Granulosa cell tumor can no longer be considered a rare neoplasm. However, because of the confusion in classification of the earlier cases reported, it is almost impossible to estimate accurately its incidence. As general interest in these neoplasms increases, the incidence seems to increase.

Since 1931 there have been many compilations on this topic, including a very masterful Monograph by J. Varangot, which is probably one of the most complete dissertations available on this subject. In their review of 160 granulosa cell tumors, Bland and Goldstein, in 1935, stated that 85 others had been reported previously, making a total of 245. In 1937, Pratt collected about 200 cases. Novak and Fauvet considered that granulosa cell carcinoma is a fairly common tumor which comprises about 10 per cent of all solid malignant ovarian neoplasms. They have studied 75 such neoplasms in their own laboratory. Recently Traut and Marchetti made a preliminary report on 61 ovarian tumors belonging to this class of neoplasms, which were collected from a group of New York hospitals.

A granulosa cell tumor may be present at practically any age. The incidence of occurrence before puberty, however, is very small.

In 1934, Bland and Goldstein collected 8 cases which occurred under the age of 11 years. Gross in his recent article states that there are 11 case reports of patients under 10 years and reports one occurring at 13 months. Up to the present time I believe that to be the youngest patient reported. Schulze in her discourse on granulosa cell tumors stated that in all probability the total number was 14. She did not include the case reported by Mannheimer of Stockholm nor Gross' recent report, so that actually 16 cases of ovarian tumors have been reported in very young children who have shown signs of precocious puberty.

The histogenesis of sex cell tumors of the ovary remains a controversial subject. The older theory that the granulosa cells were derived from the germinal epithelium has been more or less discarded by the later theories of Fischel and Meyer.

Most writers today agree that granulosa cells arise from the ovarian mesenchyme. Novak in his recent book on obstetric and gynecologic pathology, states that there is reason to believe that the histogenesis of these feminizing tumors may be traceable to a very early progranulosal, prothecal phase of development. Both the granulosa and the theca are derived from the ovarian mesenchyme, and therefore the feminizing tumors may develop with granulosal or connective tissue characteristics. Supporting this mesenchyme theory are cases reported by Klasten, Rummeld, and Compton. Recently Norris and Dunne reported a case in which a retroperitoneal recurrence was noted a number of years after the original operation for granulosa cell tumor. Voigt reported a case of primary giant granulosa cell tumor of retroperitoneal origin in a woman of 51 years of age who three years previously had undergone a supravaginal hysterectomy for a myoma. At the second operation the ovaries were found to be normal senile organs, and a large retroperitoneal granulosa cell tumor with extension into the mesosigmoid was removed. Novak concludes that both the granulosal and the thecal tumors should be included under some such designation as feminizing mesenchyma of the ovary. He also believes that the luteoma of the ovary represents merely a luteinized granulosa cell tumor.

Furth and Furth have made a very extensive report on their work with x-rays on mice, based on the probability that these neoplasms can be induced by general irradiation. Norris and Dunne conclude from their review that irradiation plays little, if any, part in the production of these tumors.

women who are thought to be "overdue." Given a patient who is "overdue," who begins to lose weight, though she may not have any other constitutional disturbances, this to me is always a danger signal for both mother and child, and may be a proper indication for induction of labor.

DR. IRVING W. POTTER, BUFFALO, N. Y.—Owing to certain procedures that we have carried on in our office for a number of years, with satisfaction to our patients and ourselves, we have never had to induce labor, and when we talk about it, we only do so to condemn it. Whether it is done by medicinal or other means, we look for the effacement of the lower uterine segment; we talk about that in preference to dilatation of the cervix and do not speak of that any more.

We do not schedule our cases either, but we deliver them at a fairly reasonable time. I simply wanted to get our position straight in the eyes of some people by saying that although we do deliver our patients at a certain time, we never induce the labor.

DR. E. L. CORNELL (closing).—I stressed the fact that this paper was devoted exclusively to the normal pregnant woman and not to cases of disproportion, the toxemic, etc. I desired to bring out the fact that women do go well past term, as we compute it, and still deliver babies that are normal.

In the entire series, there were no babies lost, no prolapsed cord, and no mother died. So far as I know, all of the babies are still living. This series only goes back about two and one-half years.

I did not say anything about the types of induction because there were so many different types utilized that it would have been necessary to take up each individually.

I recall very distinctly a woman who delivered the largest baby at the Lying-in Hospital at the time I was on the attending staff. It weighed 14 pounds and she delivered it in two or three hours.

PUBERTAS PRAECOX DUE TO OVARIAN TUMORS*

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(*From the Philadelphia Lying-In Hospital*)

ONE of the most intriguing phases of gynecology from the pathologic, endocrinologic, and clinical viewpoint, is the study of so-called "unusual tumors of the ovary." As early as 1895, Von Kahlden reported a patient with "adenoma of the Graafian follicle with transition to carcinoma." It has been generally agreed that this was probably the first authentic case of granulosa cell tumor. In 1914, Von Werdt described a tumor of the ovary as a granulosa cell type, but it was not until 1931 when Robert Meyer reported 33 such cases that interest in investigation of these tumors was stimulated. As a result, innumerable papers have been written on these and other neoplasms of various glands, such as the adrenal and pineal, which cause unusual disturbance of the normal female function. In spite of the fact that there are still many points in connection with these tumors which have not been generally agreed upon, the information which is available gives us a very much clearer concept of these conditions. It is not my desire to attempt to review completely the medical literature nor to dis-

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grades of malignancy have to be considered, although Novak believes that it is not as yet possible to base these on histologic criteria. Postoperative deep x-ray therapy is not universally considered a necessity. Many feel that x-ray therapy should be reserved for the treatment of recurrence, as it is a well-established fact that the granulosa cells are quite radiosensitive. In this way the patient's tolerance for deep x-ray therapy is maintained at its maximum and treatment can be concentrated over a limited area.

Accurate hormonal studies on these tumors are still relatively infrequent. This is probably due to the fact that the diagnosis is made only on pathologic examination when it may be too late for hormonal studies to be of value.

Schulze states that the standards for quantitative estimation vary so that attempts at comparison are very confusing. Palmer in his recent study of a tumor occurring in a 19-year-old girl also called attention to this problem. Mannheimer in the report of a granulosa cell tumor in a 4-year-old girl attempted to make a more thorough research on the hormones of the granulosa cell tumor by making a preparation of an extract of the tumor for a series of tests on animals. Unfortunately these could not be accomplished as it was impossible to produce an effective extract. In his case, the Zondek-Aschheim reaction was negative, and the percentage of prolactin in the urine was extremely insignificant. He did, however, implant one-tenth of a gram of the gland in the femoral muscles of mice which resulted in one of the animals reacting positively, and states that this may be an evidence of the fact that the tumor in question contained folliculin in greater or smaller quantities. In the case reported by Bland and Goldstein, the estrin pregnancy test was positive two days prior to operation, while the Zondek-Aschheim test was negative. Seven days post-operatively, estrin was absent. When this tumor recurred two and one-half years later in the remaining ovary, estrin was found in the blood and urine preoperatively, and the Zondek-Aschheim reaction was also positive. It is interesting to note that in the recent case report by Gross, in the follow-up six months after removal of the tumor, it was found that a twenty-four-hour specimen of urine contained 48 international units of estrogen. The breasts and the labia had regressed almost to normal size, and the pubic and axillary hair had disappeared. There was no evidence of recurrence by physical examination, and it was felt that the relatively high excretion of estrogen for a child of this age probably resulted from recurrence of the neoplasm. Pelvic exploration was therefore advised and undertaken but no recurrence was demonstrated. The uterus, also, had returned to normal size. The work of Strong, Gardner, and Hill with a transplantable granulosa cell tumor of the mouse is of especial importance. In the female hosts of the transplant there was continued estrus which disappeared after removal of the tumors. Karsner concludes that granulosa cell tumors produce estrogenic substance and quotes many case reports, but as to the continuity, the rhythm, or amount, no conclusion can be reached. He also states that it cannot be definitely said whether the condition is due to hyperestrinism or dysestrinism. Further hormonal studies with a more accurate standardized technique as advocated by Palmer should and undoubtedly will be forthcoming.

The clinical characteristics, as in other ovarian neoplasms, depend upon whether they are large enough to cause pain and discomfort. The more distinctive symptomatology is dependent upon the capability of the tumor cells to produce the estrogenic hormone. During the female reproductive period, because the secondary sex characteristics have long since been developed, there is no definite change, and the tumor merely adds quantitatively to the cyclical hormonal content of the blood. Tumors occurring during the postmenopausal age, when very little estrogenic hormone is found in the blood, produce re-establishment of periodic menstruation-like bleeding and also hypertrophy of

From a gross pathologic standpoint, granulosa cell tumors assume a variety of appearances, depending upon their size and type. Some are soft and cystic while others are semisolid or solid, depending upon the amount of tumor tissue undergoing necrosis and resulting in the formation of cystic space. It may be generally stated that it is an ovoid, solid, small, encapsulated, firm neoplasm. There is nothing characteristic in the gross appearance whereby one may know that he is dealing with a definitely malignant type of granulosa cell tumor, unless peritoneal metastasis or spread to other pelvic organs is found at operation. There is also a variability in the microscopic pattern. Novak believes that this is chiefly responsible for the confusion of nomenclature and classification of a considerable number of ovarian tumors which are now accepted as having a common histogenesis from granulosal or progranulosal tissue. The variability is exhibited not only in different tumors but in one and the same tumor, in different parts. It therefore becomes important to study numerous blocks in order to derive an intelligent impression of the tumor as a whole. Granted that numerous histologic patterns may be seen in the same tumor, one cell pattern usually predominates. The main histologic types have been described in detail by numerous authors as follicular, cylindromatous, trabecular, and diffuse.

Malignancy is still a moot question in the study of these tumors. The tumor is often called granulosa cell carcinoma and yet Karsner states that even the most gloomy statistics, unlike the data of other internal carcinomas, admit of cure in 62 per cent of the cases. He also states that it is not good practice to consider a tumor malignant merely because of its potentiality, and no more justifiable to call all granulosa cell tumors carcinomas than to classify under this same heading the mammary adenoma, the papilloma of the bladder, and other similar lesions.

In a follow-up study of 32 cases by Novak and Brawner, the clinical malignancy rate was 28.1 per cent. Huckel reports a case under observation for a period of fourteen years after operation. During this time the patient remained well and then developed a pelvic recurrence which was adherent to the uterus and small intestines. The uterus, right tube and ovary, and tumor were removed, followed by x-ray therapy. Six weeks later the patient developed a second recurrence at the root of the mesentery in the left upper abdomen, with involvement of the intestines and abdominal wall. Norris and Dunne recently reviewed a series of 24 patients treated at the University of Pennsylvania. Of these 24 patients, 10, or 45.8 per cent, survived and except for 1 patient with retroperitoneal recurrence, all have remained well varying from a period of two to twenty-two years. Seven, or 29.2 per cent, died, with death resulting in every case from known malignancy. One patient died five years after treatment from an unknown cause. Six patients have been lost. If these 6 patients are included as having died from the effects of granulosa cell tumor, the clinical malignancy rate would be 54.2 per cent which is much higher than is ordinarily attributed to these neoplasms. Norris and Dunne conclude that the granulosa cell neoplasm should not be considered too lightly with regard to the degree of malignancy. The pendulum seems to be swinging toward the malignant side after a period, during which these tumors were becoming more and more to be considered nonmalignant. The importance of the question of malignancy seems to lie in the fact that although ordinary ovarian carcinoma recurs within the first year, there are numerous cases of recurrence of these tumors many years after the original operation. It seems likely, therefore, that as in many other tumors the

cessation of the bleeding, the engorgement of the breasts would subside and the child's disposition would revert to a happier mood. Six weeks later the bleeding recurred. This period was of four days' duration, during which time a small amount of spotting occurred each day. In the interval between the periods of bleeding, a white vaginal mucous discharge was present. About this time the mother noticed a small amount of pubic hair which seemed to be definitely increasing in amount. Because of a cold, the patient was seen by the family physician, who, because of the existence of the pubic hair, made a rectal examination which revealed a mass about the size of a plum in the lower abdomen. The child was then admitted to the hospital for study. Examination on admission revealed, in addition to the enlarged breasts and pubic hair, some hypertrophy of the vulva. There was also a slight vaginal mucoid discharge. The following are the results of the studies made: The glucose tolerance curve seemed to be within normal limits. The Friedman test was negative. The urine was negative. X-ray of the head and long bones by Dr. Paul Bishop showed them to be entirely within normal limits. Study of the ossification centers showed normal development for a child of this age. The blood count was as follows: Hemoglobin, 71 per cent; red blood cells, 4,710,000; white blood cells, 8,700; differential count: polymorphonuclear leucocytes, 20 per cent, lymphocytes, 79 per cent, monocytes, 1 per cent. Hormonal studies made by Dr. Abraham Rakoff in the Research Endocrinological Laboratory, Department of Obstetrics, Jefferson Medical College Hospital, showed the following results: Sept. 5, 1939, Serum estrogen (Fluhmann), 6 to 9 mouse units per 100 c.c.; quantitative urine estrogens, 66 mouse units per twenty-four hours; serum gonadotropins, mouse units per 100 c.c., none demonstrable; quantitative urine gonadotropins, international units per twenty-four hours, none demonstrable. A tentative diagnosis of granulosa cell tumor of the left ovary was made.

On Oct. 25, 1939 operation was performed under open drop ether anesthesia. A left paramedian incision was made approximately 2 inches in length. Upon exposing the peritoneal cavity, a tumor, which proved to be the left ovary, was brought into view. The uterus was thought not to be enlarged. Inspection of the right tube and ovary showed no abnormality and the right ovary seemed to be normal in size. A left salpingo-oophorectomy was performed. Patient reacted nicely and made an uneventful recovery. She was discharged from the hospital on the eighth postoperative day.

The specimen was sent to the Ayer Clinical Laboratory of the Pennsylvania Hospital for examination and the following is the pathologic report as submitted by Dr. John Bauer, Director:

Specimen 29271.—Gross: The specimen was that of fresh tissue about 4 by 3.5 by 2 cm., somewhat ovoid in appearance. At one pole a small tortuous salpinx was attached, suggesting therefore that the mass was an ovary. The entire surface was thin, smooth, and glistening. A few small translucent cysts projected outward like small shallow vesicles, and a larger one having a blue color was noted below the surface. The vessels were not injected. Shining through the surface, the yellow color of the tissue within could be seen. On gross section no recognizable ovarian tissue could be seen. All appears to be replaced by a golden yellow tissue having an irregular lobular arrangement separated by strands of grayish white stroma and a few thin-walled cysts filled with clear slightly brown-tinged fluid. Microscopically: There were a few primordial follicles in the cortex of the ovary which was extremely narrow and surrounded the tumor. The tumor for the most part consisted of regular, small, polygonal or oval cells with even, regular, oval, vesicular nuclei, some in division. These cells appearing like granulosa cells formed a variety of patterns, some solid, some cystic. Surrounding the nodules of granulosa cells was a loose stroma of connective tissue which was reticular and traversed by a number of small, delicate capillaries and contained cells with small deeply-staining oval nuclei which were scattered throughout, chiefly at the periphery in small groups of four to a dozen or more. They suggested a derivation from the granulosa cells, comprising the main tumor but which had become separated and compressed in their extension beyond the main tumor. In other fibrous areas where these small cells were not as numerous, the connective tissue stroma appeared somewhat more condensed and apparently older. Different areas of the tumor showed a diffuse variety, a finely

the uterus. There is no demonstrable effect upon the secondary sexual characteristics. This is probably due to unreceptivity during this period. With removal of the tumor at this age, the abnormal menstruation ceases. Novak and Dworzak observed a patient who experienced a second menopause from the standpoint of vasomotor phenomena after removal of the growth. When these tumors occur during childhood, before inauguration of the normal estrogenic function, the clinical manifestations of precocious puberty are evoked; namely, precocious menstruation, hypertrophy of the breasts, the appearance of axillary and pubic hair, development of the external genitalia, and in most instances, hypertrophy of the uterus. Removal of the tumor, whether it be primary or recurrent, is followed by regression of all of these symptoms.

Novak points out that the precocious menstruation of this syndrome is an anovulatory, purely follicular type, in which respect it differs from certain other types of precocious puberty and menstruation, in which ovulation and menstruation occur. In the latter group insemination might theoretically bring about fertilization at an abnormally early age. Mengert reported an ovarian cyst which histologically appeared to be a follicular cyst, causing precocious sexual development in a child 5 years of age in whom the infantile state was resumed following operation. The pathologic discussion and photomicrograph showed no resemblance to a granulosa cell tumor.

On the other hand, granulosa cell tumors have been reported which have produced no vaginal bleeding in spite of a marked increase in estrogenic excretion. It can definitely be stated that the presence of precocious puberty with a definite ovarian enlargement is strongly suspicious of a granulosa cell tumor. During active sex life the bleeding may be present only in the form of irregularity of the menstruation so that the preoperative diagnosis can only be suspected. In the post-menopausal state, the recurrence of vaginal bleeding associated with an adnexal mass should make one at least suspicious of a granulosa cell tumor.

During the past year there have come under my observation two children, one at 9 months and one at 22 months, who had the above mentioned symptoms. Inasmuch as the first child was 4 months younger than the youngest case reported to date, and in the second child a diagnosis of granulosa cell tumor was made which proved to be a simple follicular cyst of the ovary, I should like to report these two cases in detail.

CASE 1.—G. K., 9 months of age, was referred by Dr. John Williams and Dr. William Danehower. Chief symptom was intermittent vaginal bleeding for two months, excessive growth of hair, and a lump palpable in the left abdomen. Family history was negative, there being one other apparently normal child two years older. This patient was born spontaneously. At birth she weighed 6 pounds 8 ounces and was perfectly normal, except for excessive and luxuriant growth of hair on the head, reaching almost to the shoulders. She was artificially fed without difficulty. At the age of one month she weighed 7 pounds 11 ounces and measured 27½ inches in length, was very active for her age, and her head was still covered by a dense crop of thick black hair. When she was approximately 7 months old the mother noticed some vaginal bleeding. This consisted only of spotting sufficient to cover an area about the size of a dime. Coincidental with bleeding, the mother noticed that the breasts would enlarge and the child's disposition would change. Instead of being happy and active, as usual, the patient would become irritable and restless. After

A left salpingo-oophorectomy was performed. This patient made an uneventful recovery and was discharged from the hospital on the tenth postoperative day.

The specimen was sent to the laboratory for examination, and the following pathologic report was submitted by Dr. Bauer: Specimen 29395.—Gross: The specimen in formalin consisted of a small 3 by 1 by 1 cm. fragment of ovary which contained many small cysts filled with a clear fluid. One end of the ovary was missing, this having been removed for experimental purposes. Microscopically: Near the surface were a number of immature ovules such as one sees in infants and young children. Deeper in a somewhat loose stroma were a number of cystic follicles lined by small round oval cells, suggesting granulosa cells which were heaped up in one area to form a mound in the depths of which was a tall oval granular space suggestive of an ovum but not surrounded by a zone pellucida or containing any other nuclear material. This mound of granulosa cells was suggestive of a cumulus oophorus and not suggestive of a granulosa cell tumor. There was no evidence of luteinization in any part of the section. Neither was there any evidence of a granulosa cell tumor. A low power photograph showed the cystic nature of the tumor, and a higher power photograph showed the small area of granulosa cells, suggesting a maturing Graafian follicle. On Dec. 8, 1939 Novak saw this section and said that the tissue was that of a normal ovary. Our diagnosis was ovary with follicular cysts. From the histologic appearance, it is difficult to interpret the clinical picture. I do not recall another instance of this lesion in our files and would like to hear more about the outcome of this patient.

Part of the cystic portion of the ovary was imbedded in the muscles of mice but the results were negative. During the last ten months the child seems to have been perfectly normal with no recurrence of periods or irritability. The pubic hair has entirely disappeared and although the breasts were not markedly enlarged, there seems to have been a decrease in their size.

SUMMARY

Two cases of ovarian tumors associated with precocious puberty are reported in this communication. The one tumor is what we consider to be a typical granulosa cell tumor, the other is a simple follicular cyst of the ovary. The fact that the second case responded to operative procedure and returned to normal infantile type would lead one to believe that surgery is indicated in these ovarian tumors, even though they are not of granulosa cell type.

From a review of the literature and a study of these two cases, I have no doubt that important advancements will be made, particularly with regard to the hormonal studies of this group of neoplasms.

Functioning tumors of the ovary which were formerly unrecognized, today represent a subject of such broad possibilities as to be of interest to the medical profession in general. From an endocrinologic viewpoint, these tumors furnish definite evidence of hormonal production and its clinical effects. To the embryologist, the various phases of cellular differentiation are of especial interest. The identification of these "unusual tumors" stirs the interest of the internist. The pathologist's, as well as the surgeon's, interest is concentrated upon the difficult problem of confirming the clinical diagnosis and choosing a proper course of treatment. The general interest in the study of these tumors has been stimulated to such a degree that a positive diagnosis is more likely in the majority of cases. Consequently, through proper diagnosis, pathologic confirmation and proper treatment, the prognosis today is more favorable than in the past.

folliculoid pattern, and in places a cystic pattern. Call-Exner bodies were seen chiefly in the finely folliculoid areas and in the diffuse areas. A considerable amount of lipoid was present in the granulosa cells and in the cells extending into the loose stroma surrounding the typical granulosa cell areas. The appearance of the tumor suggested the development of follicles and their attempted transformation to corpora lutea and finally to corpora fibrosa. Malcolm Dockerty and Emil Novak concur in the diagnosis of granulosa cell tumor of the ovary.

Patient's progress following operation showed a very rapid return to normal. The pubic hair disappeared, the breast engorgement subsided, and there was much less vaginal secretion. For two or three months following operation, at approximately twenty-eight-day intervals, the child became slightly irritable and had attacks of nausea. There were no other signs or symptoms of menstruation. Six months following operation further hormonal studies were made by Dr. Rakoff with the following result: May 15, 1940, Serum estrogen (Fluhmann), mouse units per 100 c.c., none demonstrable; quantitative urine estrogens, mouse units per twenty-four hours, none demonstrable; serum gonadotropins, mouse units per 100 c.c., none demonstrable; quantitative urine gonadotropins, international units per twenty-four hours, none demonstrable.

This patient was seen within the last month and seems to be well in every respect. There have been no further signs of recurrence either in symptoms or upon physical examination.

CASE 2.—C. G., 22 months of age, was referred by Dr. Ralph M. Tyson, who first attended the child when she was three weeks old. Her birth weight was 7 pounds 6 ounces. She was seen at irregular intervals during the following year and from the age of 7 months until 14 months, no medical attention was required. At fourteen months of age, she weighed 23½ pounds and was in an excellent state of nutrition. She could sit, stand, walk with help, and was alert and happy. It was at this time that enlargement of the labia and the presence of pubic hair was first noticed. Upon rectal examination it was thought that the left ovary was enlarged to about the size of the end of a thumb. There were no breast changes demonstrated. In January, 1939, the mother noticed some vaginal discharge and some blood in the urine. Urinalysis at that time revealed the presence of red blood cells. Because there had been no rapid progress in development of the secondary sex characteristics, she was kept under observation until November, 1939, when, at the age of 22 months, she was referred to me for examination. The mother stated that when the child was 17 months of age she was more restless and irritable than usual. This period of irritability which occurred in June, persisted for three days, after which time the patient seemed better. Again in August and September the patient underwent two successive periods of restlessness and irritability, during which time blood was again noticed in the urine. There had been very little development of the breasts and no increase in the amount of pubic hair. Rectal examination revealed a definite enlargement of the left ovary. The following are the results of the studies made after admission to the hospital for observation: The glucose tolerance curve was normal. Friedman test was negative. The urine was negative. The blood count was as follows: Hemoglobin, 72 per cent; red blood cells, 4,290,000; white blood cells, 5,200; differential count: polymorphonuclear leucocytes, 37 per cent; lymphocytes, 61 per cent; monocytes, 2 per cent. X-ray of the pituitary showed no evidence of abnormality, and the long bones were normal. Intravenous urography showed both sides of the urinary tract visualized, and no evidence of any gross defect present. Hormonal studies made by Dr. Rakoff showed the following results: Nov. 6, 1939, serum estrogen (Fluhmann), mouse units per 100 c.c., none demonstrable; quantitative urine estrogens, mouse units per twenty-four hours, none demonstrable; serum gonadotropins, mouse units per 100 c.c., none demonstrable; quantitative urine gonadotropins, international units per twenty-four hours, none demonstrable. A tentative diagnosis of granulosa cell tumor of the left ovary was made and operation advised.

On Nov. 15, 1939 operation was performed under open drop ether anesthesia. A left paramedian incision was made with exposure of the peritoneal cavity, revealing an enlargement of the left ovary, part of which was a very thin-walled cyst. The uterus was not perceptibly enlarged and the right ovary seemed to be normal.

At that meeting Machado talked about how to differentiate between the granulosa cell tumor, granulosa cell hyperplasia, and the theca cell tumor. These conditions do not occur alone, but each case is almost always a combination.

Two conditions have not been spoken about that produce precocious puberty, which in my experience are more common than the granulosa cells. At our hospital there have been several cases with lesions of the hypothalamus. I have recently had one in a girl who at the age of one and one-half years menstruated regularly. At the age of 3 she was so large that she had to go to school with children 5 years old. At the age of 10 she had stopped growing and the other children her age were a half head taller than she was. Now she menstruates perfectly regularly, and her condition is satisfactory in every way. Her lesion was probably of pre-pituitary or hypothalamic origin.

Then we must never forget Albright's work on early developed children who have brown spots, bone cysts, and precocious puberty. He has now collected 14 or 15 of these cases. It would be interesting to know whether the second case reported this morning had any brown spots, although her bones were x-rayed and were said to be negative. I understand that Albright has written to inquire about the child who gave birth to a baby in South America at the age of five and has been informed that that child has brown spots and bone cysts.

DR. FRANK R. SMITH, NEW YORK, N. Y.—At the Memorial Hospital we have had only 16 of these patients with granulosa cell tumors. With one exception, they had all had previous operations before coming to the hospital. I have recently had an opportunity to see a patient who five months ago was treated by the million volt x-ray machine over the tumor mass, which seemed to regress. Then a month ago I re-operated upon this patient and found not only actively growing tumor but little evidence of radiation reaction on the granulosa cell tumor. There was fibrosis of the tissue surrounding the tumor. Does Dr. Lull know of any evidence of radiosensitivity in these tumors?

DR. LULL (closing).—There was no perceptible enlargement of the uterus in either one of these cases. In women, particularly after the menopause, who have granulosa cell tumors, the diagnosis is suspected preoperatively by the fact that there is enlargement of the uterus.

This patient about whom Dr. Meigs inquired had no brown spots.

It is perfectly possible in the second case that the part of the tumor which was not examined microscopically may have had some evidence of granulosa cell tumor. The symptoms were so similar that preoperatively I felt quite certain that the second patient had a tumor of the left ovary which would prove to be of granulosa cell type.

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807 SPRUCE STREET

DISCUSSION

DR. JAMES E. DAVIS, ANN ARBOR, MICH.—Studies of pubertas praecox are limited at present to the effects produced on tissues and genital functions. The cause or causes of the hormonal imbalances are not sufficiently understood.

By accepting the origin of granulosa cell tumors as arising from the undifferentiated ovarian mesenchyme, this structure is made responsible for both stromal and follicle cells of the ovary. Functionally the mesenchyme of the ovary is cytologically sexually determined. The inherent potency is directed to utilize granulosa cells as typical feminine functioning units.

Malignancy doubtless occurs in 25 to 30 per cent of granulosa cell tumors as at present diagnosed. If the life history of all cases were completed and tissues then examined, a higher rate would doubtless prevail.

There is no reason why granulosa cell tumors should not present structural stages of malignancy similar to all other tumors and consequently be credited with unripe, midripe, and ripe cell types. This would simplify the classifications.

DR. H. M. N. WYNNE, MINNEAPOLIS, MINN.—If granulosa cell tumors could be transplanted or reproduced in experimental animals, it would be possible to test the effect of hormones antagonistic to estrin. We might also gain more knowledge of the factors involved in the growth of rests.

Dr. Lull states that in his second case hyperestrinism was not demonstrated. That portion of the ovary not examined histologically was used experimentally with negative results. Might not a very small granulosa cell tumor have been overlooked in that part of the tissue?

I have observed but one case of precocious puberty which occurred in 1916. She was a negro girl, 7 years of age. A solid tumor of the ovary was removed and a diagnosis made of carcinoma of the ovary. Several months after the operation the secondary sexual characteristics had regressed almost completely. I think this was almost certainly a granulosa cell carcinoma.

I believe our studies of the several unusual ovarian tumors might be helped by a national registry. The follow-up data over a period of years would certainly expedite our collection of facts and give us more certain knowledge of what to expect after the removal of such tumors.

DR. JOE V. MEIGS, BOSTON, MASS.—At the International Congress on Cancer held in Atlantic City last fall Novak and Machado both read papers on granulosa cell tumors. It was the opinion of most men at that meeting that it is a rather rare tumor, but Novak thought they are very common. I believe they are not very common. I have had but one case.

"Microscopically there are large pockets of neutrophiles with numerous mycelia of actinomycosis surrounded by dense granulation tissue in the ovary.

"The tube has pockets of pus in the lumen, the mucosal folds are thickened and densely infiltrated with neutrophiles and lymphocytes. No actinomycosis was found in the tube.

"The serosa of the appendix shows moderately fibroblastic proliferation plus lymphocytic infiltration. No actinomycosis could be found on repeated section."

X-ray pictures taken of the chest while the patient was still in the hospital showed no evidence of lung involvement.

The patient was seen three months after discharge from the hospital at which time she had gained ten pounds in weight. There was no evidence of any inflammatory condition whatsoever in the pelvis.

In November, 1939, one year after operation, bimanual examination revealed no evidence of any tumor masses to be felt anywhere in the pelvis. The patient's general condition was very satisfactory except for a vaginal discharge. Vaginal smears were negative for actinomycosis or trichomonas.

The patient again appeared for examination in August of 1940 with the story that in May, 1940, she developed an abscess of the occipital bone and had been referred to Rochester for surgery. A report from Dr. Love of the Mayo Clinic shows that the patient had an infection in the occipital region with evidence of increased intracranial pressure, bilateral choked discs and a diagnosis of a right cerebral lesion was made. There was a sinus in the right parieto-occipital region. Examination of pus showed no "sulfur bodies" but a *Staphylococcus albus*. She was operated upon and found to have an extensive osteomyelitis of the bone in the occipital and parietal regions. No intracerebral involvement was found. Convalescence was uneventful and her eye symptoms have improved. Our examination in September, 1940, showed small areas of granulation in the wound from which no evidence of actinomycosis could be obtained. The eye ground examination revealed no choking of the discs. An x-ray of the chest was negative. The sedimentation rate was 11 mm. per hour. The leucocyte count was 5,800. The examination of the pelvis was entirely negative and her general condition was good. So there is no evidence found of actinomycosis at the present time.

This case of actinomycosis of the ovary, being the first of its kind that I had ever seen, stimulated a review of the hospital records at St. Mary's and St. Luke's Hospitals for all cases of actinomycosis.

At St. Mary's Hospital there were only three cases to be found over a period of the last twenty years. One case followed an appendectomy with a persistent fistula and pulmonary involvement. This patient died. Another case was that of a young man of a similar type, following appendectomy, but no follow-up could be obtained on this man. There was another case involving the glands of the neck; this patient is still living. The review at St. Luke's Hospital from a period of 1923 to date revealed four cases, including the present one. Two cases were an actinomycosis of the glands of the neck; both of these patients, as far as I was able to determine, are still living. One case was actinomycosis of the bowel with a persistent draining fistula after removal of appendix. The patient finally died. The total in Duluth then, from our two leading hospitals, adds up to 3 cases involving glands of the neck, all patients living; 3 cases involving the intestinal tract and all patients are dead; and this case of actinomycosis of the ovaries, patient still living.

In a review of the literature of actinomycosis of the ovary, the theories and conjectures as to why the ovaries should be involved are exceedingly interesting. The number of cases reported in all the foreign and American literature probably does not exceed 100. Kleine, in an exhaustive review of the foreign literature, reports 80 instances in which the female organs were involved. The route of infection has been ascribed to the mouth or the intestines or the vaginal tract. In the ovary

ACTINOMYCOSIS OF THE OVARY*

W. A. COVENTRY, M.D., DULUTH, MINN.

(From The Duluth Clinic)

ON Nov. 14, 1938, Miss E. B., aged 20 years, consulted me, giving the following history:

The family history was negative. There had been no previous illness except three years prior to this time when she had had an attack of pain in the lower right quadrant which lasted for two weeks. There was fever; she was observed at her local hospital and treated expectantly. In the three-year interim she had been very well. Her present complaint was that seven days previously she had had a pain in the lower right quadrant of the abdomen, radiating into the right groin, not related to the menstrual period. At this time she vomited. She was transferred to her local hospital (in another city) and was under observation for three days. There was no particular abdominal tenderness. Her temperature was 101° F. but fell to normal the next day. The pain promptly disappeared and she was sent home. Three days later the pain reappeared and she came under my observation. The pain was intermittent in the lower right quadrant of the abdomen. It was associated with loss of appetite. Constipation had been the rule.

At the time of our first observation, the blood pressure was 104/60. Except for a leucocytosis of 28,700 the blood counts were essentially negative. The urinalysis was negative. The blood Wassermann was negative. The heart and lungs were normal to auscultation and percussion. There was some slight tenderness in the lower right quadrant of the abdomen. There was no rebound tenderness, and it was not suggestive of an abscess or appendicitis. Bimanual examination revealed the uterus in good position and normal size. In the right adnexa one could feel a mass which was diagnosed as a possible pus tube. Smears for Neisserian organisms were negative, and possible exposure was denied.

She was referred to St. Luke's Hospital for further observation and on Nov. 21, 1938, she was operated upon by me. Upon opening the abdomen there was a peculiar odor, suggestive of colon, but not typical. Further examination revealed a pelvic inflammatory mass involving the right tube and ovary. The left tube and ovary were normal. The sigmoid and cecum were normal. The gall bladder was negative to palpation. The appendix was postperitoneal, lying in the midline. The uterus was also normal in size and negative for tumors. It was felt that the mass on the right side was a tuboovarian abscess. The mass which included the tube and ovary was removed without breaking into the capsule. The appendix was removed in the usual manner. The patient made an uneventful recovery with primary union. She was discharged fourteen days later.

The report of the pathologist, Dr. A. H. Wells, was as follows:

"The ovarian mass is somewhat rounded and slightly nodular, with an irregular outer surface. It is 7 by 6 by 4.5 cm. The outer surface was a dull gray, and there is evidence of old fibrous adhesions. These adhesions bound the tube down to the surface of the ovary without closing the ampullar end. The cut surface of the ovary is made up of irregular, thick, trabeculae of fibrouslike tissue between which there are numerous pockets of thick, grayish and, after fixation, granular purulent matter. There is no evidence of normal appearing ovarian tissue in the mass. The lumen of the tube is small and apparently empty. The fimbriated end is open.

"The appendix is 4.5 cm. long, the lumen of which is slitlike or obliterated throughout.

*Presented at the Fifty-Third Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons at Excelsior Springs, Mo., September 26 to 28, 1940.

METASTASES

Metastases are reported by some writers to be actually blood borne. It may spread to any part of the body, even the bones. Whether my patient had an extension to the occipital region remains to be seen. At any rate sulfur granules were not found and the wound has entirely healed without any further incident. According to the averages found by most authors as far as cures are concerned, usually some metastatic involvement occurs at some time or another. Needless to say, this patient is so located, near my town, that it will be possible to observe her from year to year.

TREATMENT

The treatment seems to vary from surgical treatment to the use of x-ray and iodides. Many authors think that these patients should have deep therapy and many think they should not. X-ray seems to be particularly helpful, according to Vonessin, in the more superficial actinomycotic lesions, especially those in the cervicofacial area, but he also believes that they should have more intensive treatment than most inflammatory lesions. I think treatment depends entirely upon the location.

Many authors think that iodine should be given to saturation over a long period of time, and there are many who are of an opposite opinion.

Surgery seems to enter into the picture in all cases. In this particular case, I think I have been very fortunate in being able to isolate the specimen, to remove it in toto, and no other treatment has been instituted. The patient is living and well two years later without any apparent evidence of recurrence.

SUMMARY

I have presented the case of a young girl with no characteristic symptoms of actinomycosis, who was operated upon. A tumor of the right ovary was found adherent to the right tube, with no involvement of the appendix, cecum, uterus, or parametrium. The tumor was removed in toto. The pathologic diagnosis is actinomycosis with no areas of actinomycosis found in the tube or appendix. It is hard to conceive that this could be a primary actinomycosis of the ovary; surely there must be some primary source of infection. It may be from the mouth, it may be blood borne, it may be through the intestinal tract through the walls without any scars being observable. At any rate, the case is most interesting, and two years later the patient is very well indeed.

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DISCUSSION

DR. FREDERICK H. FALLS, CHICAGO, ILL.—This subject is of special interest to this society because of the rarity of the lesion; because of the infrequency with which the correct diagnosis is made clinically, and because of its high mor-

one wonders whether it may come from the intestinal tract or whether it is direct communication from the genital tract. Kleine believes that the ovaries are affected through contact with the intestinal tract, augmented by the susceptibility of the broken tissues in follicular rupture. Actinomycosis of the ovary must be secondary to some port of entry. A primary infection of the ovary is not reasonable. In this case, however, the cecum and the appendix showed no evidence of primary infection, although one writer is firmly convinced that actinomycosis may invade and pass through the cecum without leaving any evidence or scars remaining after the invasion or the passing through the walls of the cecum, and thus it secondarily involves the ovary. There have been only one or two cases of involvement of the uterus primarily. Jaffé thinks that cases of involvement of the female organs are increasing. Involvement of the parametrium need not necessarily mean involvement of the uterus; it may spread to the parametrium via the ovary. He believes that it is usually secondary to infection of the intestines. One author reports a small abscess of the cervix where actinomycosis was found. Another author reports a case of a woman in the poultry business, who had a prolapse of the uterus, in whom actinomycosis of the uterus developed.

It is generally agreed that an actinomycotic infection by the vaginal route is probably a very remote and very rare occurrence. Strangely enough most of the cases reported occurred in the right ovary, which again leads to the opinion that it is an intestinal infection that is the primary source, because the appendix and cecum are the most common sites in the alimentary canal.

Falls is of the opinion that the grasses and grains, as a source of infection, are somewhat remote; the organism does not form spores but fragmentates, and it is not resistant to heat, cold, or dryness.

Joseph and Summerill report a case of actinomycosis of the right ovary in which the tube was involved. It was their contention that it was the result of a vaginal infection following delivery.

Côté and Tudhope report four cases of actinomycosis of the ovary in which they noted the peculiar appearance of the ovary as found in my case. One could not make the diagnosis until the ovary had been sliced and gave the characteristic appearance as described by the pathologist in my case, i.e., "irregular thick trabeculae of fibrous-like tissue between which are numerous pockets of thick grayish granular purulent material."

V. H. Cornell reported a case which was of long standing before coming under the proper observation. He reviewed the literature also and found 71 published cases of actinomycosis, 45 of which were dead, 8 of them improved, and 7 in which the outcome is doubtful and only 11 which are possible cures.

Rosow was firmly convinced that most cases arise from the bowel. Cordua seems to differ from Falls' opinion and he says that actinomycosis is widespread in moist and dry earth and that the spores are easily transported by the winds to the grasses, grains, vegetables, and fruits, and also found in butter and cheese, the feces of man and animals, and even the teeth of healthy persons, and yet the disease is quite rare. He is inclined to think that actinomycosis is nonpathogenic for most people.

One would like to call this case a primary actinomycosis of the ovary, but how could such an incident happen without more definite proof than we have, in spite of the fact that this case showed no involvement of the appendix or cecum or tubes.

terectomy was done with the removal of both ovaries and both tubes. The endometrium, the mucosa of both tubes and both ovaries showed a definite infection with the ray fungus.

The incision from this operation healed very well and the pelvic condition has not recurred to date. However, the fistulous tracts in the abdominal wall continued to extend, involving both sides of the abdominal wall from the pubic spine on each side to well above the anterior superior spines and into both flanks. The fistulous tracts were opened and drained many times, and she was given a number of x-ray treatments and huge doses of potassium iodide over a period of four years. There was considerable improvement from the above treatments, but the fistulas persisted. As everything except very radical surgery had failed, it was decided to dissect out these huge sinuses, some of them ten inches long and involving the muscles and other tissues down to the peritoneum. This was followed by large doses of potassium iodide, and by September, 1938, all sinuses were healed, and she has remained quite well to the present time.

DR. COVENTRY (closing).—So far as reinfection is concerned, this may spring up anywhere. It is interesting to find in the literature how frequently it occurs in bones. It does occur, of course, also in the lungs.

The case of Dr. Smead's is the usual story of a patient not coming early and sinuses forming. In any postoperative patient where there is a persistent sinus, the first thing to think of is not foreign bodies but an actinomycosis.

tality rate. Cornell found 71 cases up to 1934; of these, 45 died and only 11, or 15 per cent, were probably cured.

I wish to emphasize that the lesion is found on the right side practically always first, and that it may and often does extend to the opposite side after the removal of the primary lesion. The left ovary and tube are usually not involved at the time of the first operation. The question naturally arises as to the value of a prophylactic panhysterectomy under these circumstances. My opinion is that if there is extensive involvement of the ovary on one side, the fundus of the uterus and the opposite tube and ovary should be removed. The obvious difficulty is the uncertainty of the diagnosis from the gross appearance of the ovary.

It is practically impossible to diagnose the condition clinically until abscess with sinus formation and cultivation of the organism on blood agar slants reveals the typical growth. It is important to note that bacteriologically the growth first is noticed in seven to nine days. This is dry and scaly, and grows with a raised dirty grayish brown border. At operation an inflammatory lesion involving the right ovary or tube and ovary, without evidence of a similar process at work on the opposite side, should make the gynecologist very suspicious that the case is one of actinomycosis. From what I have seen and read of the disease, I should be inclined to do a supracervical panhysterectomy and to avoid spilling any of the pus if possible. I also would feel inclined to place these patients on full doses of potassium iodide and follow the operation with therapeutic x-ray treatments.

I am inclined to classify Dr. Coventry's case as one of primary actinomycosis of the ovary for the reasons he has given and also for the reason that, if some other site of infection had been present, it would probably not have lain dormant during the months and years since operation.

Dr. Coventry is to be congratulated on the outcome of his case to date. It must be remembered, however, that this is a treacherous disease and it is not yet too late for such a misfortune to occur in his case, although highly improbable. I was highly gratified with the immediate postoperative results of the first case of this kind that I observed. But when the lesion recurred on the opposite side and when x-ray and potassium iodide failed to arrest the growth, I became less optimistic.

My second experience with this disease was in May of this year. The woman was 43 years of age, had had the left tube and ovary removed five years previously for ectopic pregnancy. She developed right lower quadrant pain a year and a half before and had metrorrhagia for three months. On examination a rectal fistula was found on the left side of the anus. At operation the uterus was seen to contain a small fibroid, and there was a tumor mass in the region of the right ovary. A supracervical hysterectomy with removal of the ovarian tumor was done.

The ovary measured 4 by 5 by 4 cm. and contained two cystic spaces. The ovary was moderately firm, and on section there were areas of yellow tan tissue. Microscopic sections of the ovary showed an enormous round cell granulation tissue reaction in which well-defined "sun-rayed" and clubbed fungi of actinomyces were found.

Following operation, she developed a pelvic abscess which drained into the bladder and which closed spontaneously. Two weeks later she returned to the hospital with an infected abdominal wound. We were unable to cultivate the actinomyces from the pus from this abscess. Two other abdominal sinuses formed later; she gradually lost weight and strength, in spite of x-ray and potassium iodide in full doses. Sulfanilamide was tried without result and she died June 5, 1940.

DR. LEWIS F. SMEAD, TOLEDO, OHIO.—In 1933 I saw a woman, aged 30 years, with an abscess in her right side. She had been the secretary of a nationally known medical man who had done a lot of experimental work on actinomycosis and had later died of the disease.

In May, 1932, she had been operated upon for what was supposed to be acute appendicitis. In March, 1933, I found her with an abscess under her operative scar which I opened and drained. This was followed by a fistula which refused to heal. She later developed a chronic pelvic inflammatory disease and finally came to operation in July, 1933. Both adnexa were involved, and a supracervical hys-

largely upon the judgment of the individual operator, it seemed best to base this presentation on a limited personal experience rather than to include a much larger series of patients operated upon by others as well as myself. There were 39 instances of adenomyosis; 10 of adenomyoma; 63 of "chocolate" ovarian cyst and widespread endometriosis, and 3 of endometrioma (Table I).

TABLE I. PERSONAL PATIENTS WITH ENDOMETRIOSIS OPERATED UPON WITHIN TEN YEARS

Adenomyosis of uterus	39
Adenomyoma of uterus	10
"Chocolate" ovarian cyst and widespread endometriosis	63
Endometrioma	3
	115

I have seen a number of additional patients in whom a tentative diagnosis of endometriosis seemed warranted, but whose annoyances were not intolerable. The use of progesterone has apparently helped to keep some of these young women comfortable. Another group of women presented clinical evidence of the disease during operation, but since the pathologic reports on the excised tissue failed to verify the diagnosis, all such cases have been excluded from this presentation.

SYMPTOMATOLOGY

The chief symptoms in all forms of endometriosis seem to be abnormal bleeding, pelvic pain, and acquired dysmenorrhea. (Table II).

TABLE II. SYMPTOMS OF ENDOMETRIOSIS IN 115 PATIENTS

71 patients, or 61 per cent, had pain
71 patients, or 61 per cent, had abnormal bleeding
18 patients, or 15 per cent, had dysmenorrhea

Pain, or a sensation of pelvic pressure, may be generalized throughout the pelvis or elsewhere; in the suprapubic region, one of the lower abdominal quadrants, or the sacral area. Dyspareunia is a common complaint, particularly when the structures behind the posterior vaginal fornix are involved. When the rectovaginal septum is indurated by endometriosis, increasing constipation, painful defecation, or a consciousness of rectal pressure may also be noticed by the patient. In some instances the pain radiates down one or both thighs. Abnormal bleeding initiated by endometriosis is characterized by menorrhagia, shortened intermenstrual intervals, or clots. A few patients had a little dirty brown uterine discharge between their menstrual periods, but no one mentioned bright red intermenstrual bleeding.

Dysmenorrhea may be premenstrual, intramenstrual, or postmenstrual. It is sometimes accompanied by vomiting and fainting, and is invariably of recent origin rather than primary.

Other symptoms observed in occasional cases are urinary frequency, leucorrhea, and evident abdominal tumor. Concomitant fibromyoma occurred in a large number of cases, 46 times in 115 cases, or 40 per cent.

THE TREATMENT OF PELVIC ENDOMETRIOSIS*

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EVERYONE doing a large number of pelvic operations must have been impressed by the apparently increasing incidence of endometriosis found in recent years. If Sampson's theory of retrograde tubal cellular spill is applicable in the majority of instances, it seems logical to suggest that the pernicious custom of plugging the vaginal lumen with cotton and other fibrous material during menstruation by the modern woman may be a causative factor. Long before the elegant and much advertised manufactured products were marketed, some women had improvised absorbent cotton occlusions to enable them to dispense with vulvar pads. The different theories of Von Recklinghausen, Cullen, Sampson, Meyer, Robinson, and other authoritative students of endometriosis, regarding its etiology, are well known and require no further elaboration. Although endometriosis is no longer a clinical enigma, its complex nature is not yet fully understood, and the susceptibility of certain women to this disease remains a mystery. Suffice it to say that while the majority of cases are probably due to reversed menstrual flow, a few others may originate as rests of coelomic epithelium, by perforation of hemorrhagic ovarian cysts, by direct implantation, and possibly by lymphogenous or hematogenous dissemination. The term endometriosis is used to include adenomyosis and adenomyoma of the uterus; extrauterine endometrial implants anywhere in the pelvis; involvement of the rectovaginal septum; chocolate cysts of the ovary; endometriosis of bladder, appendix, and colon; endometrioma; and abdominal wall implants following previous laparotomy, particularly after Gilliam's suspension operation and cesarean section. All of these varieties are characterized by the same physiologic response to the hormonal influence of the ovaries as the uterine endometrium. Dougal and others have suggested that by grouping all cases under the headings "internal endometriosis," when the lesions are confined within the visceral peritoneum of the uterus, and "external endometriosis," whenever the glands are found elsewhere, the other designations used for the protean manifestations of what is essentially a uniform pathologic process can be discarded. Unfortunately such a simple classification provides for no distinction between circumscribed tumefactions and a diffuse heterotopia, nor for their locations. Hence, I believe that it is desirable to retain those terms which possibly convey a definite conception of each individual case.

During the past ten years prior to July, 1940, I have operated upon 115 women suffering from endometriosis. Since the treatment of such cases constitutes a surgical problem and the technical details depend

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severe menorrhagia and pelvic pain. In an effort to be justly conservative I split the myometrium and enucleated the tumor with some difficulty, assuming that I was doing a myomectomy and preserving menstruation and the childbearing function. Only after the specimen reached the laboratory was it evident that I had eviscerated the uterus,

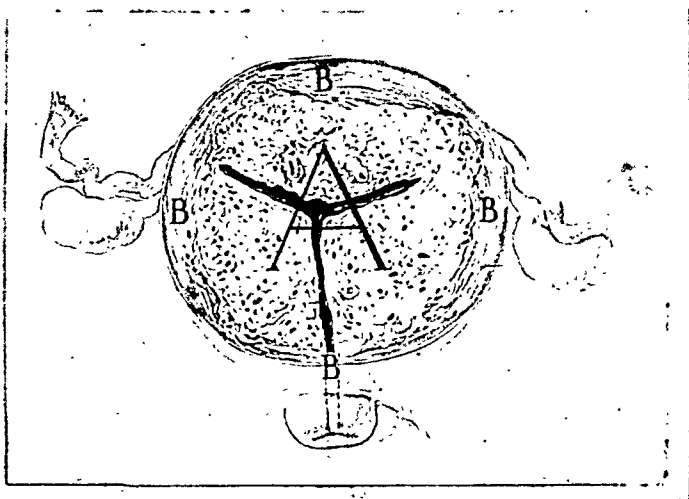


Fig. 2.—Huge symmetrical adenomyoma in a 28-year-old patient, simulating a fibromyoma. A, adenomyoma; B, shell of myometrium.

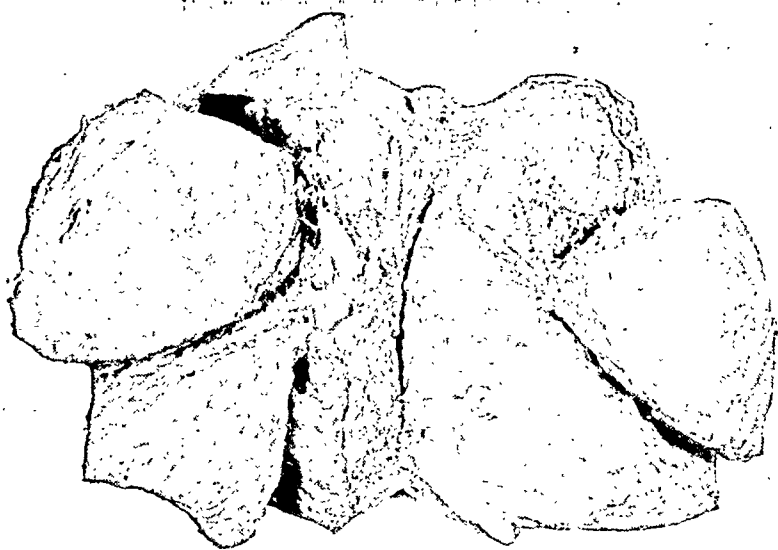


Fig. 3.—Large adenomyoma, previously treated unsuccessfully by another gynecologist with 1500 mg. hours of radium therapy for the control of profuse bleeding.

and that the tumor was an adenomyoma (Fig. 2). Despite the retention of both normal ovaries, this patient has, of course, never menstruated since the operation, as the entire endometrial cavity was included in the extirpated tumor. In two of these cases the adenomyoma encroached upon the bladder to such an extent that hysterectomy was difficult, and

ADENOMYOSIS

Adenomyosis implies a diffuse penetration of the myometrium by typical and benign endometrial glands. In reviewing these 39 cases of adenomyosis, without other endometrial lesions, the patients' ages are noteworthy. Only 2 were less than 35, one being 31 and the other 34. The rest ranged from 35 to 56 years, so that ovarian conservation was seldom a serious problem. Every one was subjected to hysterectomy; 34 supravaginal, 4 total, and 1 vaginal in a patient with an incidental procidentia. One or both ovaries were retained in a few patients in whom the diagnosis was not established until the laboratory report was received. One patient had been unsuccessfully treated with roentgen ray therapy for the control of menorrhagia, and another was operated upon three years after a laparotomy for tubal gestation. The diagnosis

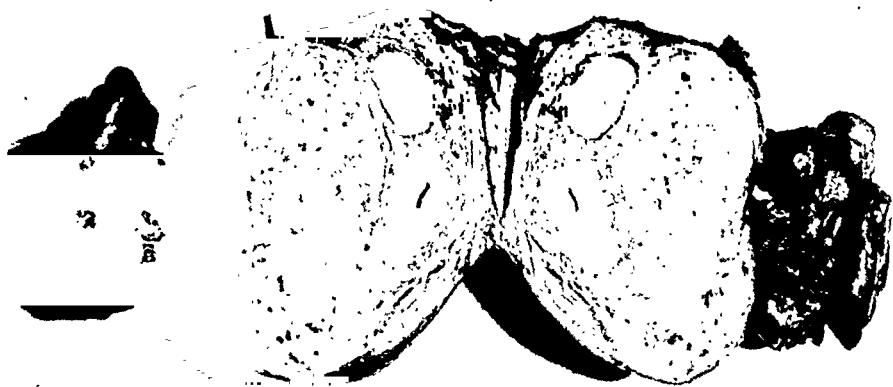


Fig. 1.—Typical adenomyoma of the uterus.

of adenomyosis can be made positively only after uterine extirpation, and it is quite possible that many additional cases are unknowingly and successfully treated with intrauterine radium therapy. In this group of 39 patients treated surgically, the end results were satisfactory.

ADENOMYOMA OF UTERUS

The term adenomyoma of the uterus is applied to a circumscribed nodular area or tumefaction of the myometrium consisting chiefly of endometrial glands (Fig. 1). Grossly it simulates a fibromyoma and, when encountered without evidence of endometriosis elsewhere in the pelvis, may be easily mistaken for an ordinary fibroid. I made this error in 6 of the 10 cases in the series, although 4 of them also showed areas of adenomyosis scattered through the uterine corpus, and 5 of them were accompanied by true fibroids. All but one patient was more than 36 and less than 40 years of age. The exception was a young woman of 28 with a huge symmetrical tumor of the uterine corpus, which produced

and two others had been unsuccessfully treated elsewhere with roentgen ray therapy for menorrhagia. It would, therefore, seem that whereas intrauterine radium therapy may be effective in the treatment of adenomyosis, the value of x-ray treatment in some cases of both adenomyoma and chocolate ovarian cysts is questionable.

One patient, 55 years old, operated upon four years previously and still living, had a large papillary adenocarcinoma within a huge chocolate cyst (Fig. 4). Another patient had bilateral multilocular chocolate cysts, in the largest of which there was a benign papillary cyst adenoma (Fig. 5). Chocolate cysts are due to endometrial implants involving the ovary with ensuing hemorrhage, and must be differentiated from corpus luteum hemorrhagic cysts. They can be distinguished



Fig. 4.—Papillary cyst adenocarcinoma formed in the wall of a large chocolate cyst. The papillae are covered with several layers of columnar epithelium. (Multiple chocolate cysts were present.)

from the latter by the evidence of intracystic repeated hemorrhages, irritation in the adjacent structures, and one or two points of rigidity in the cyst wall, which represent the site of the implant. One had a picturesque involvement of the vaginal fornix with blue dome cysts (Fig. 6). Four showed endometriosis of the appendix, and in one of these, aberrant endometrial glands were found in the muscularis, as well as on the visceral peritoneum (Fig. 7). Extension beyond the uterovesical peritoneal fold and into the bladder musculature occurred in two cases, distorting the uterovesical peritoneal reflection in much the same manner as in the two cases in which an adenomyoma infiltrated the bladder wall. Hysterectomy without bladder damage may be extremely difficult under such circumstances, but vesical resection is unnecessary, as the mucosa escapes involvement and ovarian ablation will be followed by rapid retrogression of the lesion. Implants were discovered in the Fallopian tubes in five other cases. In another woman there were extensive im-

one of them subsequently developed a urinary fistula, which required a second laparotomy for closure. Another patient with a large adenomyoma (Fig. 3) had been previously treated unsuccessfully by another gynecologist with 1,500 mg. hours of radium therapy for the control of profuse bleeding. Coincidentally, chocolate ovarian cysts and involvement of the rectovaginal septum were found in three cases. In general, it can be said that the majority of cases of adenomyosis and adenomyoma of the uterus are found in women of more than 35 years of age; that some form of hysterectomy is necessary for cure; and that conservation of ovarian function is usually a matter of little importance. When unpleasant menopausal symptoms appear, replacement organotherapy affords prompt relief. A follow-up of my 49 patients indicates a satisfactory end result when so treated.

CHOCOLATE OVARIAN CYSTS AND WIDESPREAD ENDOMETRIOSIS

The surgical treatment of widespread pelvic endometriosis is a challenge to the judgment of every operator, principally because 40 per cent of cases occur in women of less than 35 years of age (Table III).

TABLE III. AGE INCIDENCE IN WIDESPREAD PELVIC ENDOMETRIOSIS

	NUMBER OF PATIENTS	APPROXIMATE PER CENT
25-35 years	25	40
36-60 years	38	60

Many gynecologists favor routine radical procedures, including the removal of all ovarian tissue, thus cutting off completely the stream of estrin supply, and thereby insuring prompt regression of implants and protection against reoperation for subsequent extension of the disease. My own practice has been to perform either a supravaginal or total hysterectomy in patients more than 35 years of age, but to conserve as much normal tissue as possible in younger women, and I have so far had no reason to regret it. I believe that it is better to risk the necessity of another operation, than to castrate young women indiscriminately for any benign condition.

In the 63 cases under consideration there were chocolate cysts of the ovary in 56 patients, scattered implants in 24, involvement of the rectovaginal septum in 17, and associated adenomyosis in 9 (Table IV).

TABLE IV. INVOLVEMENTS IN 63 CASES OF WIDESPREAD PELVIC ENDOMETRIOSIS

		APPROXIMATE PER CENT
Chocolate ovarian cysts	56	90
Scattered implants	24	38
Rectovaginal septum	17	27
Associated myometrial adenomyosis	9	15

Chocolate cysts of the ovary were found in women from 25 to 60 years of age. Two patients with large cysts had been subjected to supravaginal hysterectomy with bilateral ovarian retention by other operators,

plants in the wall of the colon, a condition which makes complete ovarian removal imperative to prevent subsequent obstruction and to re-establish the gut lumen. It is of paramount importance to differentiate endometriosis from an annular carcinoma of the bowel without palpable metastases, to avoid a superfluous intestinal resection.

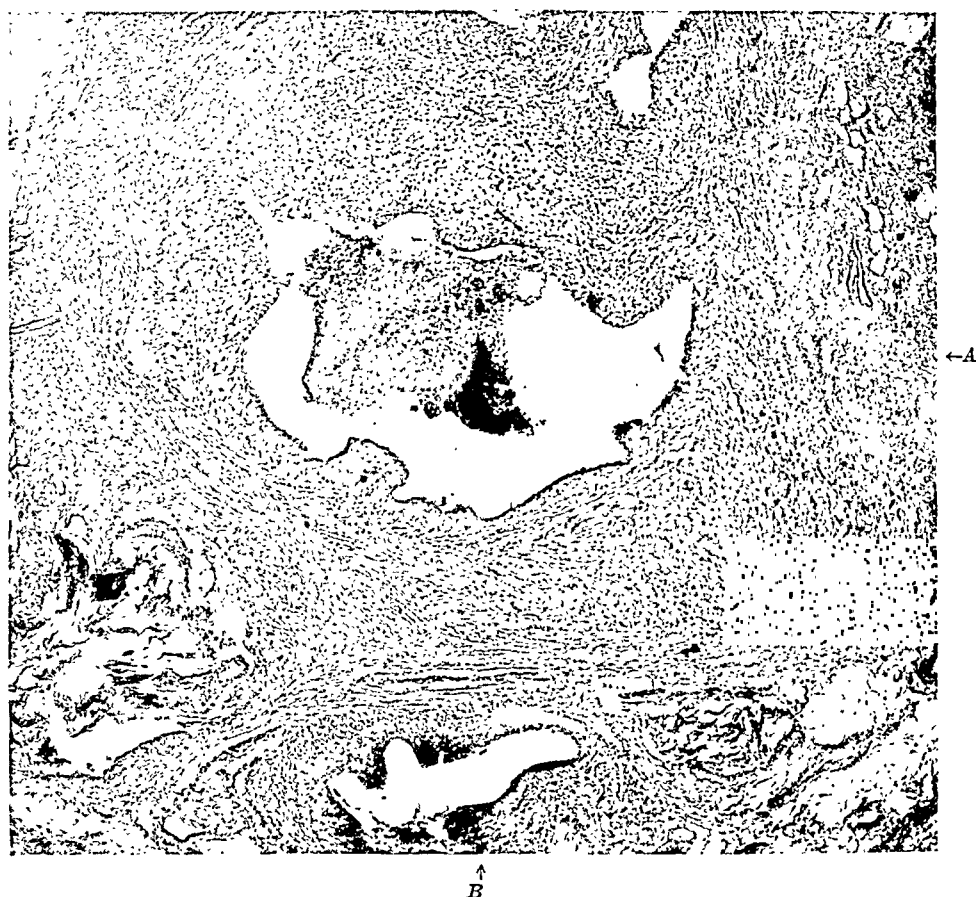


Fig. 7.—Endometriosis of the appendix. A, points to an endometrial cyst in the musculature, filled with blood. B, points to a similar cyst in adhesions between the appendix and oviduct.

In the group of 38 women more than 35 years of age, I removed all ovarian tissue in 32 cases and conserved one or part of an ovary in 6. Supravaginal or total hysterectomy was done in all of these, except the two women whose uteri had been removed previously by another operator. On the other hand, in a group of younger patients, those of 35 years or less, every effort was made to preserve some ovarian tissue (Table V).

TABLE V. OPERATIVE PROCEDURES FOR CHOCOLATE OVARIAN CYSTS AND ENDOMETRIOSIS IN PATIENTS LESS THAN 35 YEARS OF AGE

Unilateral oophorectomy	7
Removal of one ovary and resection of the other	7
Myomectomy and unilateral oophorectomy	4
Hysterectomy and unilateral oophorectomy	2
Hysterectomy and bilateral oophorectomy	5
	25



Fig. 5.—Benign papillary cyst adenoma in wall of chocolate cyst, 18 by 18 by 6 cm. The columnar epithelium imitates endometrial glands and the stroma resembles endometrial stroma.

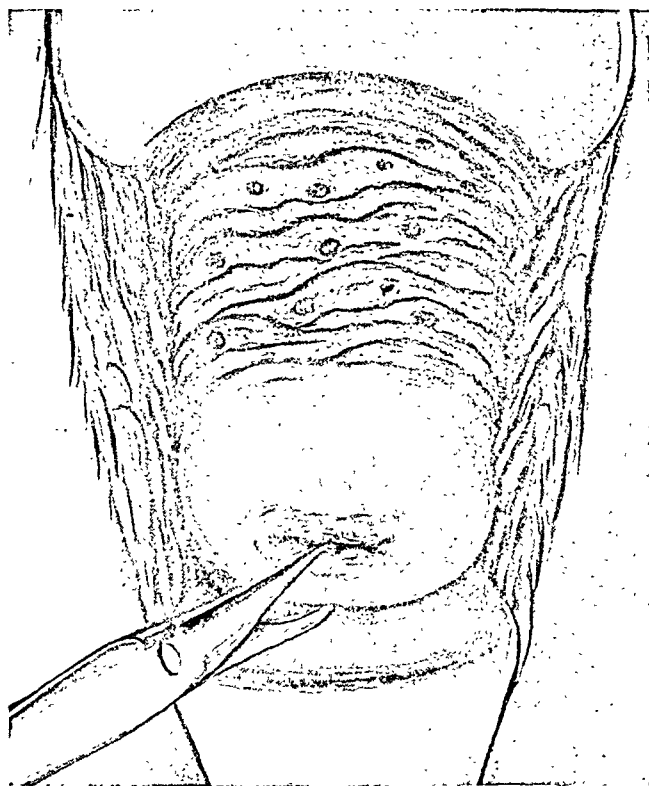


Fig. 6.—Blue dome cysts of the posterior vaginal fornix, filled with chocolate material.

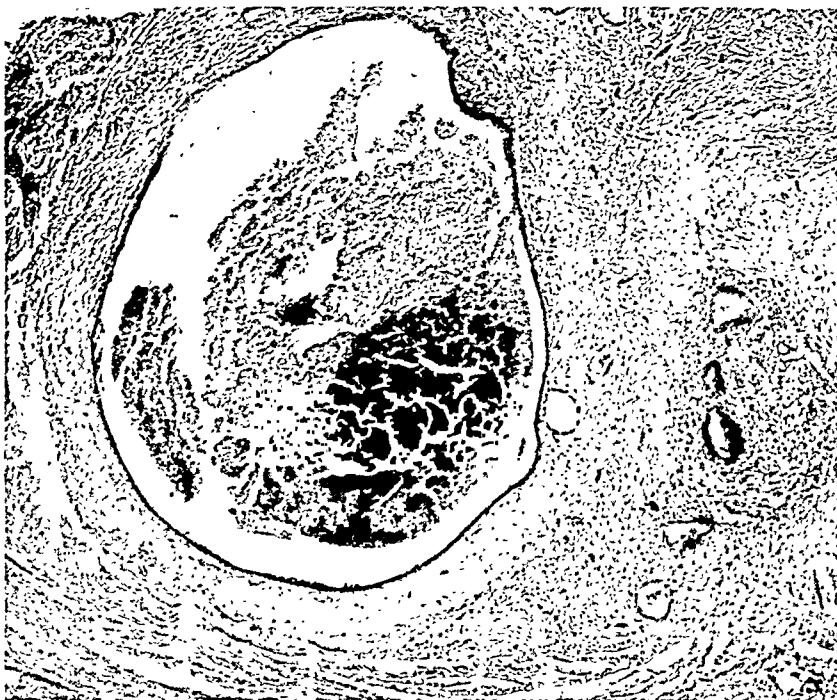


Fig. 9.—Endometrioma of the abdominal wall after a Gilliam suspension. The cysts are lined with endometrial epithelium, the largest being filled with blood.



Fig. 10.—Subserous nodule in the left broad ligament, attached to the uterine cornu, oviduct, and ovary. The tubules are lined with endometrial gland epithelium.

In 5 instances the involvement of the pelvic structures was so extensive that ablation of the uterus and both adnexa was imperative. More radical surgery is justifiable when the cul-de-sac is densely indurated, but small implants can be destroyed with a fine wire cautery tip. All patients have been conscientiously followed up, but to supplement the records a letter was sent to each of the other 20 young women, asking each to state (1) whether or not she has been well since her operation, (2) whether she has been subjected to another operation elsewhere, and (3) if she has been pregnant since her operation. Replies have been received as follows: all are well but 2, who have moderate pelvic pain and dysmenorrhea. None has required a secondary operation, and 2 have delivered at term, one eighteen months, and the other two years after operation. This incidence of 10 per cent pregnancy is not so insignificant as it may seem, since 4 of the patients were unmarried.

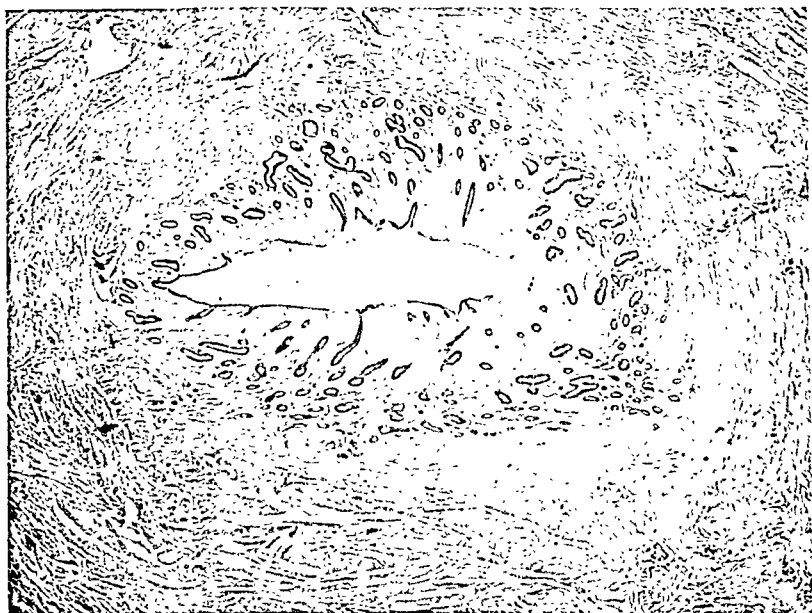


Fig. 8.—Endometrioma of the round ligament. The cyst is lined by endometrium with well-formed glands.

ENDOMETRIOMA

An endometrioma may be defined as a circumscribed tumor, consisting chiefly of endometrial glands extraneous to the uterus, ovaries, and Fallopian tubes. Three such cases were found.

A 23-year-old, unmarried girl was operated upon because of severe menorrhagia, secondary dysmenorrhea, and pain in the right lower abdominal quadrant. In addition to the removal of a large simple serous cyst of the right ovary and the appendix, a nodular mass intrinsic in the right round ligament, about 4 cm. from the uterine cornu, was excised. This tumor, about the size of a hickory nut, proved to be an endometrioma (Fig. 8).

A 34-year-old, unmarried woman presented herself, complaining of severe pain and swelling during each menstrual period, in a tumefaction in the abdominal wall. This patient had been subjected to a modified Gilliam suspension operation of the uterus elsewhere three years previously. A round mobile endometrioma, about the

CONCLUSIONS

1. The use of progesterone has apparently contributed to the comfort of some young women suffering from endometriosis whose annoyances were not intolerable.
2. Pelvic pain, abdominal bleeding, dysmenorrhea, and dyspareunia are the most common symptoms of endometriosis.
3. Concurrent fibromyomatous tumors were found in 40 per cent of cases.
4. The majority of cases of adenomyosis and adenomyoma are found in women of more than 35 years of age, and hysterectomy is necessary for cure.
5. Forty per cent of cases of chocolate cysts and widespread pelvic endometriosis occur in women of less than 35 years of age, and normal ovarian tissue should be conserved in these young women.
6. Intrauterine radium therapy may be effective in the treatment of adenomyosis, but the value of roentgen ray therapy in cases of adenomyoma and chocolate cysts is questionable.
7. Vesical resection is unnecessary and dangerous in the treatment of bladder wall infiltration.
8. Complete ovarian extirpation is essential for the cure of bladder and intestinal wall involvements.
9. Certain technical operative details which have been described will simplify the operative procedures.

DISCUSSION

GEORGE VAN S. SMITH, BROOKLINE, MASS.—At the Free Hospital for Women we have also had a low operative mortality, 4 deaths among 734 patients with endometriosis treated to date, 0.54 per cent, despite the fact that so often the disease makes operation technically difficult. I wonder whether the low mortality may not be partly accountable to increased peritoneal resistance resulting from more or less constant irritation by the process.

Headache associated with menstruation, sometimes severe, migraine-like and incapacitating, is a symptom I would emphasize as often characteristic of the disease. A history of such cyclic headaches is useful in the differential diagnosis. Furthermore, I have gained the impression that patients with endometriosis are generally highstrung, more than usually nervous and under high internal tension. This impression receives support from their social history, namely, 10 per cent of the married patients in our series were separated or divorced. Parenthetically, 40 per cent were childless. I would tend to blame the disease for the tense state of their nervous systems, for, after all, they have true vicarious menstruation, they have an increased menstruating area without an outlet and so take more menstrual punishment, as it were.

I question the rationale of administering progesterone to these women, beyond the fact that Dr. Dannreuther found it helpful for some with a presumptive diagnosis of endometriosis. Although I have had no experience with hormone trials in this disease, it would be interesting to employ testosterone with the aim of producing temporary inactivity of the ovary and hence endometrium-bearing areas. But would the regression of the ectopic endometrium be permanent? Certainly the hormone would not affect the adhesions and scarring resulting from the disease and to which so much of the symptomatology is attributable. Conceivably the giving of testosterone might be a diagnostic and possibly a therapeutic test and might be of value for postponing operation in a younger patient or as a preoperative measure to put the internal genitalia at rest. I would not want to lean upon hormone therapy more than temporarily in the treatment of endometriosis, both because

size of a walnut, was located 6 cm. to the left of a lower midline abdominal scar. When excised, it was found in proximity to the site of the round ligament attachment, involving the muscle and fascia (Fig. 9).

A 38-year-old, married woman was subjected to supravaginal hysterectomy and bilateral salpingo-oophorectomy for chocolate cysts and numerous endometrial implants throughout the pelvis. A nodular intraligamentary tumor, simulating a parasitic fibroid in the left broad ligament, proved to be an endometrioma. There were no fibroids in the uterus (Fig. 10).

TECHNICAL DETAILS

It would be presuming for me to suggest the adoption of standardized surgical procedures for the operative treatment of endometriosis. I shall therefore mention only a few technical details which have proved of apparent value in my hands. The most important of these is to defer the actual pelvic operation until the pelvic organs have been freed from all omental and intestinal entanglements, and the normal anatomic relationships have been restored so far as possible. Manipulations designed to mobilize the pelvic viscera should be started by the dissecting hand in the deepest possible recesses of the cul-de-sac and continued upward. Dissecting maneuvers, either sharp or blunt, begun at the top of the agglutinated area result in shredding of tissue, extensive bleeding, and difficulties in general. When a huge tumor mass is impacted in the true pelvis, a longitudinal incision on the anterior aspect of the uterine corpus will facilitate the removal of much of the tumor bulk by either enucleation or morcellation. This permits a lateral collapse of the myometrium, and gives free access to the ovarian and uterine vessels. On the other hand, if the mass is intraligamentary, it can be partly or completely mobilized quite easily by making a parallel incision just below the course of the round ligament and gently detaching the parametrium with the fingers. Chocolate cysts are often extremely thin walled and inadvertently ruptured. The prompt use of suction enables the operator to dispose of the cyst contents immediately and clears the operative field nicely. If the uterovesical fold of peritoneum and the bladder wall are densely infiltrated, it is important to remember that it is wiser to leave some of the uterus attached to the bladder than to jeopardize the bladder wall by overenthusiastic separation. This principle also holds true when the lower uterine segment and rectum are extensively involved. In conservative ovarian procedures in young women, especially after ovarian resection, it has seemed advantageous to shorten the uteroovarian ligament, thus elevating the remaining tissue out of the pelvis and maintaining its position close to the uterine cornu. In some cases there may be remaining areas which cannot be satisfactorily peritonized. Under such circumstances I have utilized one or two sheets of gutta-percha tissue to wall off the intestinal coils and omentum from the pelvis. In the presence of persistent oozing from some raw surface, a gutta-percha cigarette drain with a long iodoform gauze end is of great value. Attempts to clamp and ligate every small bleeding point are futile and a waste of time. All of these drains are brought out of the lower angle of the abdominal wound, removed after forty-eight hours, and have evidently been of service in the prevention of subsequent intestinal obstruction.

We have done presacral neurectomies in 10 of the conservatively treated patients but cannot draw any worth-while conclusions as yet. Counsellor has done it in 13 instances and feels that it prevents pain with recurrences, but since the nerve supplies only the uterus and bladder, it would seem that it cannot play a large part in the symptomatology. The neurectomy is done as the first step and the peritoneum closed before separating the pelvic adhesions to avoid retroperitoneal implantation.

Pyogenic infection of a chocolate cyst is a serious complication, for it does not tend to resolve, acting like the ovarian abscesses found in ordinary pelvic inflammation. The adhesions are so dense that one cannot do any extensive surgery without great danger of damaging intestine and spreading infection. It is a rare complication fortunately. My procedure is to drain the abscess and use x-ray treatment after the inflammation has quieted down. In the last one I did the patient still had symptoms from her adhesions, and the hysterectomy done ten months after the original infection proved to be surprisingly easy.

If a patient has had both ovaries removed for endometriosis, should one use estrogen if her climacteric symptoms are bad? It might stimulate renewed growth of the tumor and the patient should be examined frequently. So far I have seen only one questionable bad effect. A woman of 45 had a hysterectomy and bilateral salpingo-oophorectomy done for chocolate cysts. I saw her again two years later complaining of abdominal pain and showing nodules in the posterior cul-de-sac by vaginal examination. A gastrointestinal x-ray was negative. She refused operation, x-ray treatment had little effect, she developed masses throughout the abdomen and died in a few months. No autopsy was allowed. A review of the specimen removed at operation showed no cancer.

She had been treated most of the time for a year with estrogen, but I could not find out how much was used. This is a very inconclusive story, I realize, but it suggests that the estrogen may have stimulated some implants to growth and that cancer developed in them. I think one should be cautious in the use of estrogen for climacteric symptoms after operations for endometriosis.

580 PARK AVENUE

THE EFFECT OF COMBINED ADMINISTRATION OF CHORIONIC GONADOTROPIN AND THE PITUITARY SYNERGIST ON THE HUMAN OVARY*

PRELIMINARY REPORT

CHARLES MAZER, M.D., AND ELKIN RAVETZ, M.D., PHILADELPHIA, PA.

IT IS now definitely established that the three phases of the ovarian cycle, follicular maturation, ovulation, and luteinization, are evoked by the successive and harmonious action of the two anterior pituitary sex hormones, known as the follicle-stimulating and the luteinizing fractions.

The individual and combined effects of the two pituitary sex hormones are better discernible in hypophysectomized than in normal infantile animals, because even the immature hypophysis of most species contributes to the response of the ovaries to treatment with the gonadotropins. Thus, injections of the follicle-stimulating fraction in rats, five to fifteen days after pituitary ablation, evoke growth of the ovarian follicles but no luteinization. Whereas, injections of the luteinizing principle in hypophysectomized rats causes neither follicular growth nor

*Read in abbreviated form at a meeting of the Texas Association of Obstetricians and Gynecologists, October 5, 1940, and as here presented at a meeting of the Philadelphia Obstetrical Society, November 7, 1940.

of its own pathology and because of its associated pathology. Thus, 50 per cent of our series had fibroids, 7 patients had cancers outside the pelvis, 4 of which were in the breast, 7 had cancer of the cervix, 7 had cancer of the endometrium, and 50 had associated ovarian tumors, of which 15 were malignant, a 5 per cent incidence of ovarian cancer in those with endometriosis over the age of 40. In one instance endometrioma, benign papillary cystadenoma and cancer were found in the same chocolate cyst. Furthermore, in reviewing the microscopic sections of 401 of our series treated before 1935, I found 18 instances in which papillary change was clearly evident in the stroma, indicating that the chocolate cyst was changing into a papillary cystadenoma, a tumor which has marked propensity toward further change into malignancy.

DR. F. A. PEMBERTON.—Regarding etiology we are inclined to feel that transformation of the surface epithelium of the ovary and of the peritoneum play a larger part in chocolate cysts and pelvic sites than is generally supposed and that there may be an endocrine factor also. The disease seems to be more common in single women and in married women who have practiced contraception. Sixty-five per cent have a functional-like menorrhagia and more than half have headache at menstruation. Furthermore, fibroids are a common coincidental finding. Counsellor says that if there is a marked cystic hyperplasia of the endometrium in the uterus the endometriosis will be too extensive for conservative treatment and that, as would be expected, the endometrium in both sites shows the same picture.

Thirteen per cent of our patients showed no tumors in the ovaries, a finding which is well known, but I think it is not generally appreciated that it may happen so often.

The number of different locations of the disease is extraordinary. Its appearance in the cervix and vagina is easily understood, but why is it found so rarely, considering the great number of patients who have a dilatation and curettage followed by plastic operations on the vagina? We have seen only one instance of a perineal tumor following such operations. It may be that endometrium during menstruation has some quality which favors implantation, having been primed with the ovarian hormones perhaps and, since plastic operations are rarely done at that time, endometriosis does not follow.

We are struck by the backache which those patients having the tumor in the uterosacral ligaments complain of. It is fairly constant and much worse during menstruation, and may be present when examination reveals only tenderness in the ligaments with no palpable tumor. It has helped me in making a diagnosis.

We treated 470 patients, proved by pathologic examination, at the Free Hospital for Women up to 1936. We did conservative operations on 30 per cent of them.

If the patients want children, as they often do, we make every effort to save the uterus and some ovarian tissue, being careful to destroy all the implants, that cannot be easily removed, with the fulgurating needle. The patients are followed, and if recurrences appear and careful consideration makes us feel that another conservative operation is not indicated, we use x-ray treatment. We have been struck by the early recurrence in five cases, that is, within two to five months. It seemed as if the operation spread and stimulated the growth.

One reason for doing conservative operations is to conserve fertility. Eighty-three were married and under 40, and 19 (22 per cent) became pregnant, but only 2 of them more than once. It seems to us therefore that, everything else being equal, if a patient has had several children, conservation of fertility is not important since she is likely to have only one more child.

We have been surprised by the low mortality. There was only 1 death, that from pulmonary embolism, in the 470 cases, 329 of which had a supravaginal or complete hysterectomy, and 141 a conservative operation of some type. They were operated upon by the various members of the staff. When one considers the dense adhesions so often dealt with and the trauma to the pelvic wall in the region of the iliac veins, one would expect more thrombotic complications. Perhaps it is a sign of gentleness in handling and of cutting rather than tearing adhesions whenever possible. This low mortality seems to indicate that chocolate cysts are not infected very often.

gonadotropic hormone also stimulates development of immature rat ovaries (gauged by weight and microscopic appearance) to a far greater degree than could be expected by any additive effect resulting from the use of the two constituents individually. They, therefore, suggested that the element responsible for this effect is present in the hypophysis of the immature rodent as an inactive prohormone which is converted into an active substance by the addition of chorionic gonadotropin.

The observation of Evans that pituitary extracts almost totally free from the follicle-stimulating hormone enhance the activity of chorionic gonadotropin was corroborated by Mazer and Katz⁹ in 1933. The latter, moreover, obtained no greater ovarian weight by combining chorionic gonadotropin with a pituitary extract relatively rich in the follicle-stimulating hormone. The results were the same, provided the two dissimilar pituitary extracts represented an equal quantity of pituitary tissue. This observation suggested that it is not chiefly the follicle-stimulating principle which enhances the activity of chorionic gonadotropin but rather an unknown substance in the pituitary extract.

Recently, we obtained from the Research Laboratory of Parke, Davis & Co. freshly prepared extracts of human pregnancy urine (chorionic gonadotropin) and of anterior pituitary lobe tissue, both of which we employed individually and in combination in groups of infantile rats, weighing 30 to 40 Gm. The ovaries of such rats normally have an average weight of from 10 to 12 mg. As seen in Table I, a total of 0.3 mg. of the chorionic gonadotropin preparation, or of 1 mg. of the pituitary extract, employed individually, increased the weight of the ovaries of each of the two groups of test animals to an average of 24 mg., only double that of the controls. However, when the same quantities of the two extracts were given in combination to a group of infantile rats, the average weight of the ovaries increased to 99.4 mg., eight times that of the control animals. Furthermore, it required 8 mg. of the chorionic gonadotropin preparation or 10 mg. of the pituitary extract to produce a 500 per cent increase in the ovarian weight of the immature rats; but the combination of only 0.1 mg. of the chorionic gonadotropin preparation and 0.3 mg. of the pituitary extract produced such a 500 per cent increase. These results cannot reasonably be attributed to a physiologic expression of the combination of the follicle-stimulating and luteinizing principles.

TABLE I. EFFECT OF CHORIONIC GONADOTROPIN AND THE PITUITARY SYNERGIST EMPLOYED INDIVIDUALLY AND IN COMBINATION UPON IMMATURE RATS*

CHORIONIC GONADOTROPIN		PITUITARY SYNERGIST		COMBINATION		
TOTAL DOSE	WEIGHT OF OVARIES	TOTAL DOSE	WEIGHT OF OVARIES	TOTAL DOSE OF CHORIONIC GONADOTROPIN	TOTAL DOSE OF PITUITARY SYNERGIST	WEIGHT OF OVARIES
0.15 mg.	22.4 mg.	1 mg.	23.0 mg.	0.075 mg.	0.25 mg.	50.3 mg.
0.3 mg.	24.3 mg.	2 mg.	42.6 mg.	0.1 mg.	0.3 mg.	58.6 mg.
0.6 mg.	29.0 mg.	4 mg.	47.7 mg.	0.15 mg.	0.5 mg.	70.4 mg.
1.0 mg.	28.3 mg.	6 mg.	43.2 mg.	0.3 mg.	1.0 mg.	99.4 mg.
5.0 mg.	39.5 mg.	8 mg.	48.1 mg.			
6.0 mg.	49.5 mg.	10 mg.	55.2 mg.			
8.0 mg.	63.2 mg.					
10.0 mg.	72.5 mg.					

*Average weight of control infantile rat ovaries, 10 mg.

Each determination represents the average ovarian weight of each of 5 infantile rats

luteinization of the granulosa cells. When, however, the two fractions are administered either in succession, first the follicle-stimulating and then the luteinizing fraction, or concurrently, the ovaries of hypophysectomized rats undergo follicular ripening, ovulation, and luteinization.

THE PHARMACOLOGIC ACTION OF THE COMMERCIALY AVAILABLE GONADOTROPINS

A gonadotropin is an ovarian and testicular stimulant, regardless of its source. The available gonadotropins are derived from animal pituitaries, pregnant mare serum and human pregnancy urine.

Animal pituitaries yield mostly the follicle-stimulating hormone, very little of the luteinizing principle. The separation of the two hormones is not only difficult but also impractical, because both elements are needed to produce a complete ovarian cycle. Pituitary gonadotropic extracts, if given in sufficient quantity, evoke follicular growth, ovulation, and luteinization in the ovaries of intact immature and hypophysectomized animals alike. They are, however, insufficiently concentrated for therapeutic use.

The blood of pregnant mares yields a considerable quantity of gonadotropin which is effective in both the intact and hypophysectomized test animal. It is, therefore, believed to be identical with the sex hormones of the anterior hypophysis.¹ The equine gonadotropin is, moreover, sufficiently concentrated to produce multiple ovulation in some women.^{2, 3} Clinically, equine gonadotropin seems to be most effective in the treatment of sterility due to anovular menstruation. In its present concentration, it is, however, almost useless in the treatment of the more common menstrual disorders, amenorrhea and dysfunctional uterine bleeding.

Human pregnancy urine yields a luteinizing principle derived from the placenta. It is, therefore, known as chorionic gonadotropin. In the ovaries of most intact species, it produces all of the effects of pituitary and equine gonadotropins. It is, however, incapable of stimulating to any appreciable degree the ovarian follicles of hypophysectomized animals, intact monkeys, and human beings.^{4, 5} It is, therefore, assumed that the pituitaries of animals other than the monkey and the human being contribute, in some unknown manner, to the ovarian response to chorionic gonadotropin.

The undoubted therapeutic value of chorionic gonadotropin in many instances of dysfunctional uterine bleeding must, for the present, be attributed to a mechanism independent of the ovaries.

EARLIER EXPERIMENTS WITH COMBINED CHORIONIC AND PITUITARY EXTRACTS

The observation of Leonard⁶ in 1931, that a combination of chorionic gonadotropin and a pituitary extract rich in the follicle-stimulating principle produces in intact immature rats ovarian weights averaging 142 per cent greater than the sum of the increased weights produced by each component individually, was accepted as evidence of the physiologic expression of the combined action of the two gonadotropic principles. Evans and his co-workers^{7, 8} observed, however, that the combination of chorionic gonadotropin and hypophyseal extracts relatively free from

TABLE II. GROSS AND MICROSCOPIC APPEARANCE OF THE OVARIES OF 23 WOMEN WHO RECEIVED PREOPERATIVELY INJECTIONS OF A COMBINATION OF CHORIONIC GONADOTROPIN AND THE PITUITARY SYNERGIST

RECORD NO.	AGE	TOTAL NUMBER OF SYNERGY UNITS	DURATION OF PREOPERATIVE TREATMENT	TIME RELATION OF EXPECTED FLOW TO LAPAROTOMY	GROSS APPEARANCE OF OVARIES		MICROSCOPIC APPEARANCE OF OVARIES		TYPE OF ENDO-METRIUM
					RIGHT	LEFT	RIGHT	LEFT	
A18983	45	150	5 days	15 days	Small and sclerotic	2 large hemorrhagic follicles	Sclerosis	2 early corpora lutea	Secretory
A19238	32	150	5 days	10 days	1 corpus luteum	3 clear follicles	1 corpus luteum	Not excised	Secretory
A19876	35	315	14 days	1 day	Moderately enlarged; 2 corpora lutea and 3 hemorrhagic follicles	Serous cyst	Not excised	Serous cyst	-
A19552	42	315	7 days	7 days	3 hemorrhagic follicles	2 hemorrhagic follicles	1 corpus luteum and 2 hemorrhagic follicles	2 hemorrhagic follicles	Secretory
A20035	43	180	6 days	11 days	Large serous cyst; 1 large hemorrhagic follicle	3 hemorrhagic follicles	Serous cyst; 1 early corpus luteum	2 hemorrhagic corpora lutea; 1 hemorrhagic follicle	Secretory
A20207	46	180	6 days	18 days	Sclerotic	Enlarged; 1 corpus luteum and 4 hemorrhagic follicles	Old corpus luteum	Fresh corpus luteum; 4 hemorrhagic follicles	Proliferative
A20450	28	270	12 days	1 day	Both ovaries the size of tangerines; distended with many hemorrhagic follicles	Both ovaries the size of tangerines; distended with many hemorrhagic follicles	1 corpora lutea in various stages of development	Not excised	Secretory
A20443	31	210	7 days	7 days	Both ovaries the size of average lemons; studded with many hemorrhagic follicles	Both ovaries the size of average lemons; studded with many hemorrhagic follicles	1 corpus luteum; many hemorrhagic follicles beginning luteinization	Not excised	Secretory
A20511	35	90	2 days	16 days	1 corpus luteum	Dermoid cyst; 3 hemorrhagic follicles	Not excised	Dermoid cyst; 2 small corpora lutea, 2 hemorrhagic follicles	-
A20948	43	60	One injection	Metrorrhagia 23 days	Sclerotic; 1 hemorrhagic follicle	3 hemorrhagic follicles	Not excised	Not excised	-
A21022	12	60	One injection	23 days	No hemorrhagic follicles	No hemorrhagic follicles	Not excised	Not excised	-

Knowing that even nonspecific substances, such as egg albumen and zinc sulfate, can convert the follicle-stimulating hormone into a luteinizing principle,¹⁰ it is reasonable, in the light of the facts cited above, to suspect that there is some unknown element in the pituitary component of the extracts employed which renders chorionic gonadotropin so much more potent.

EXPERIMENTS ON THE HUMAN BEING POINTING TO THE EXISTENCE OF A PITUITARY SYNERGIST

The most important indication that the anterior hypophysis probably produces a substance which converts the species-selective chorionic gonadotropin into a universal gonadotropin is the phenomenal response of the human ovary to a combination of chorionic gonadotropin and a pituitary extract containing very little of gonadotropic activity, because neither of the two administered individually exerts the slightest influence on the human ovary. Chorionic gonadotropin, regardless of its concentration, does not stimulate the human ovary; the available pituitary gonadotropins are insufficiently concentrated for use in the human female. Nevertheless, the combined administration of the two seemingly inert extracts produces a degree of stimulation of the human ovary far in excess of the normal requirement.

The product we employed in 23 patients preoperatively is, as stated above, a combination of chorionic gonadotropin and a pituitary extract containing very little of gonadotropic substance (Table I). It is commercially known as synapoidin. One cubic centimeter of synapoidin yields 15 synergy units. A synergy unit is the minimum quantity which, when given in 6 divided doses over a period of three days, increases the weight of the ovaries of infantile rats 500 per cent. The pituitary component in the synergy unit of synapoidin is only one-thirty-fifth of the quantity which, when employed alone, is capable of evoking a similar increase in weight of the ovaries of infantile rats. The chorionic gonadotropin component of the synergy unit of synapoidin is only a seventy-fifth of the quantity that gives a similar ovarian response in infantile rats.

Twenty-three patients, varying in age from 12 to 46 years, were each given 75 to 315 synergy units over a period of from one to eighteen days before laparotomy for various gynecologic conditions. Twenty of the twenty-three patients showed macroscopic evidence of stimulation in the form of oversized ovaries, multiple hemorrhagic follicles, and, in many instances, multiple incompletely-formed corpora lutea. Only one of the 16 patients in whom one or both ovaries were removed at operation failed to show microscopic evidence of intense stimulation.

The degree of the ovarian response seems to depend upon the receptivity of the ovaries, the total dosage and the duration of treatment. Thus, the ovaries of three regularly menstruating, young women in this group were overstimulated to a pathologic degree. In each, the ovaries were 8 to 10 cm. in diameter and studded with numerous hemorrhagic follicles which ruptured and bled at the slightest touch. The uteri were enlarged, soft and congested, simulating early pregnancy. However, in premenopausal women, the ovarian response apparently varies inversely with the degree of pre-existing sclerosis. In some, one

ovary was definitely stimulated, though not much enlarged, while the corresponding ovary remained small and highly sclerotic. In a girl, 12 years old, a single injection of 125 synergy units three days before operation for subacute appendicitis evoked no changes that could be discerned by mere inspection. In another girl of the same age, the preoperative administration of double the quantity, spread over a period of five days, caused a considerable increase in the size of the ovaries and the appearance of several hemorrhagic follicles (Table II).

Careful microscopic study of the removed ovaries of 16 patients revealed multiple hemorrhagic follicles with luteinized granulosa layers in all but one. Multiple small and large aberrant corpora lutea, hemorrhage into the stroma, and intense edema were present in the ovaries of some of the younger patients. In other words, in young normally functioning women, the larger doses caused a profound disruption of the whole follicular apparatus. The microscopic appearance of the overstimulated ovaries approximated that observed by Hartman¹¹ in monkeys which received large doses of equine gonadotropin with or without the chorionic luteinizing principle.

Concerning possible deleterious effects resulting from such treatment, Hartman states: "It is, therefore, a justifiable conclusion that the manifestly deleterious action of the extracts employed is temporary, and that recovery is prompt and complete. No facts have come to light which would lead one to condemn the use of gonadotropic extracts in attempts to help sterile women when they are desperately desirous of having children."

In 11 of 14 patients in whom hysterectomy or curettage of the uterus was performed simultaneously, the endometrium showed a pronounced secretory phase; in two, the endometrium was only proliferative in type though the ovaries contained fresh corpora lutea; in the remaining 1 of the 11 women in this group, the endometrium was atrophic and the ovaries sclerotic despite adequate preoperative treatment. This does not imply that the secretory endometrium in the 11 patients was the result of treatment, for only one of them was frankly amenorrheic.

For obvious reasons, the preoperative treatment with synapoidin was short in most of the 23 patients. In planning the use of the product for therapeutic purposes, one should seek to imitate the normal length of the human menstrual cycle and administer the product in smaller doses for twenty days of the month.

CLINICAL EVALUATION OF SYNAPOIDIN THERAPY

Therapeutically, we have thus far employed synapoidin in only 49 carefully selected patients. Those treated for mild forms of menstrual disorders are not included in this report. Twenty-three of the patients had varying degrees of persistent amenorrhea; 18 were suffering from severe menorrhagia or metrorrhagia; and 8 were sterile mainly because of failure of ovulation.

Effect on Amenorrhea.—Of the 23 amenorrheic patients, 3 had never menstruated and 11 had not menstruated for one or more years. Only 9 of the group had one to three periods during the year preceding treatment with synapoidin. All of them had previously been treated by other means, without relief.

A21514	42	180	7 days	14 days	Enlarged; 1 corpus luteum and 4 hemorrhagic follicles	Enlarged; 3 hemorrhagic follicles	1 fresh corpus luteum; 3 hemorrhagic follicles	3 hemorrhagic follicles one undergoing luteinization	Late proliferative
A21519	41	210	10 days	5 days	Both ovaries the size of lemons; distended with many hemorrhagic follicles		2 corpora lutea; 2 hemorrhagic follicles	Not excised	Secretory
A21520	43	120	4 days	Amenorrhea	3 hemorrhagic follicles	1 corpus luteum; 2 hemorrhagic follicles	3 hemorrhagic follicles, 1 beginning luteinization	1 corpus luteum; 2 hemorrhagic follicles	Secretory
A21567	32	120	8 days	7 days	1 corpus luteum; 4 hemorrhagic follicles	1 corpus luteum; 3 hemorrhagic follicles	Not excised	Not excised	-
A20559	33	180	4 days	Amenorrhea	4 hemorrhagic follicles	1 corpus luteum; 4 hemorrhagic follicles	Many hemorrhagic follicles, some showing beginning luteinization	Not excised	-
A21986	41	180	12 days	Amenorrhea	Small and sclerotic	Small and sclerotic	Sclerosis	Not excised	Proliferative
A22053	34	150	7 days	1 day	Enlarged; 4 hemorrhagic follicles	1 corpus luteum and 1 hemorrhagic follicle	Not excised	1 corpus luteum and 1 hemorrhagic follicle	Secretory
A22275	44	195	6 days	Metrorrhagia	Enlarged; 3 hemorrhagic follicles	Size of lemon; 2 large hemorrhagic follicles	2 corpora lutea and 1 hemorrhagic follicle	1 corpus luteum and 1 hemorrhagic follicle	Secretory
A22380	45	240	10 days	1 day	1 large and 1 small corpus luteum	1 small corpus luteum	2 fresh corpora lutea	1 old corpus luteum	Secretory
A22447	14	120	5 days	1 day	Enlarged; 1 large corpus luteum, and 1 hemorrhagic follicle	Enlarged; 1 large hemorrhagic follicle	Not excised	Not excised	-
A22557	24	240	12 days	3 days	Both ovaries size of oranges, deep blue in color, oozing blood from many points		Not excised	Not excised	-
A23188	42	165	5 days	8 days	2 corpora lutea; 4 hemorrhagic follicles	Dermoid cyst	1 corpus luteum; 4 hemorrhagic follicles, 2 with beginning luteinization	Dermoid cyst	Secretory

of 10 injections of 30 synergy units each. Excluding the four patients who proved totally resistant to this form of therapy, 45 courses of injections in the remaining 19 patients thus far evoked menstrual bleeding 38 times (Table III). An 84 per cent response to single courses of injections is very encouraging, *since it implies renewed ovarian activity and not merely withdrawal bleeding as in estrogen replacement therapy*. We must, nevertheless, remember that these results are far from conclusive, since only 2 of the 23 amenorrheic women have thus far menstruated without treatment. The majority of them are still under treatment.

From our limited experience in the treatment of severe cases of amenorrhea, it appears that injections of this product should be given in gradually reduced doses thrice weekly for twenty days of each month for a period of six consecutive months. The individual dose of the first and second courses of treatment should, in our opinion, be no less than 30 synergy units. From a more extensive experience in the treatment of the milder forms of amenorrhea (oligomenorrhea), it appears that half of the above-mentioned dose given similarly over a period of three months is sufficient in most instances.

Effect on Dysfunctional Uterine Bleeding.—The results with one course of from 5 to 20 injections of similar doses in 18 patients suffering from dysfunctional menorrhagia or metrorrhagia are more striking than in amenorrhea. The patients varied in age from eleven to thirty-nine years and were bleeding abnormally for a considerable length of time. In 14 of the 18 patients, the bleeding was arrested during a follow-up period of from two to six months (Table IV). Four of these 14 were puberal girls in whom uterine bleeding is so often most resistant to all forms of therapy until nature establishes a normal pituitary-ovarian balance.

TABLE IV. RESULTS OF TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING IN EIGHTEEN PUBERAL GIRLS AND WOMEN OF CHILDBEARING AGE

PATIENT	AGE	TYPE OF BLEEDING	MONTHS OF BLEEDING	SIZE OF DOSE	NO. OF DOSES	PRELIMINARY CURETTAGE	RESULT	MONTHS OF FOLLOW-UP PERIOD
M. B.	33	Metrorrhagia	3	30 u.	10	None	Relieved	5
B. B.	14	Metrorrhagia	1	30 u.	10	None	Relieved	4
S. G.	11	Metrorrhagia	1	30 u.	10	None	Relieved	2
N. H.	19	Menorrhagia	10	30 u.	10	None	Not relieved	
M. K.	35	Menorrhagia	10	30 u.	11	None	Relieved	2
H. P.	27	Menorrhagia	6	30 u.	10	None	Not relieved	
H. M.	24	Menorrhagia	24	30 u.	5	None	Relieved	2
G. S.	18	Metrorrhagia	1	30 u.	6	None	Relieved	2
M. L.	14	Menorrhagia	8	45 u.	10	None	Relieved	3
E. L.	27	Metrorrhagia	2	30 u.	6	None	Relieved	2
S. M.	33	Metrorrhagia	1	30 u.	15	None	Relieved	4
L. R.	31	Metrorrhagia	1	30 u.	10	None	Relieved	3
S. M.	31	Metrorrhagia	1	30 u.	5	Hyperplasia	Not relieved	
R. R.	21	Metrorrhagia	2	30 u.	10	Proliferative	Relieved	4
A. S.	27	Metrorrhagia	2	30 u.	5	Atrophic	Relieved	2
C. W.	17	Metrorrhagia	3	30 u.	20	None	Relieved	3
J. Z.	20	Metrorrhagia	4	30 u.	5	None	Relieved	3
M. B.	24	Metrorrhagia	30	15 u.	20	None	Not relieved	

Anovular Menstruation.—Only 2 of 8 women with anovular menstruation as the chief cause of sterility conceived soon after synapoidin treatment. They received 5 injections, each 15 synergy units, during the first half of the menstrual cycle and conceived promptly. Most of the others received larger doses which, in the light of our observations during laparotomy, overstimulate the normal and partly active ovaries to a pathologic degree. This is also suggested by the fact that the larger doses either shortened or lengthened the menstrual interval, depending on the time in the cycle at which treatment was terminated. Thus, if the larger doses were

Amenorrheic patients received 5 to 10 injections of 30 synergy units of synapoidin every other day. Second or third courses were given soon after the cessation of an induced menstrual flow or, in the event of failure, about two weeks after the last injection.

Regardless of the duration of the amenorrhea, only 4 of 23 women failed to menstruate after one or two courses of injections. In fact, one of the patients, aged 20, who had never menstruated, had her first menstrual flow five days after the last

TABLE III. AVAILABLE DATA ON THE TREATMENT OF TWENTY-THREE SEVERELY AMENORRHEIC WOMEN

PATIENT	AGE	NO. OF MEN- STRUAL PERIODS DURING YEAR PRE- CEDING TREATMENT	TYPE OF AMEN- ORRHEA	SIZE OF DOSE	NO. OF INJEC- TIONS PER MONTH	NO. OF MONTHS TREATED	NO. OF INDUCED MEN- STRUAL FLOWS	COMMENT
B. C.	24	0	Second- ary	30 u.	15	1	0	Treatment in progress
R. D.	29	0	Second- ary	30 u.	8	2	2	Treatment in progress
A. E.	24	0	Second- ary	15 u.	10	2	2	Treatment in progress
H. F.	25	0	Second- ary	30 u.	9	2	2	Treatment in progress
E. G.	19	3	Second- ary	30 u.	6	3	2	No spontane- ous periods
L. H.	23	3	Second- ary	30 u.	7	3	2	No spontane- ous periods
F. H.	19	0	Second- ary	30 u.	10	2	2	Treatment in progress
N. L.	20	1	Second- ary	30 u.	5	5	5	Treatment in progress
G. V.	27	0	Second- ary	30 u.	5	1	1	No follow up
E. C.	36	1	Second- ary	30 u.	8	2	1	Treatment in progress
G. M.	27	0	Second- ary	30 u.	10	2	2	Treatment in progress
G. G.	27	3	Second- ary	30 u.	8	2	2	Treatment in progress
F. B.	27	0	Second- ary	30 u.	7	3	1	No spontane- ous periods
J. R.	17	2	Second- ary	30 u.	10	2	1	No spontane- ous periods
A. R.	30	3	Second- ary	30 u.	5	2	0	No spontane- ous periods
R. S.	28	3	Second- ary	30 u.	7	3	3	Treatment in progress
C. S.	28	0	Second- ary	45 u.	6	2	2	4 spontaneous periods
H. W.	28	0	Second- ary	45 u.	5	2	2	No spontane- ous periods
R. D.	20	0	Pri- mary	30 u.	10	2	1	Treatment in progress
L. K.	30	2	Second- ary	15 u.	10	2	2	2 spontaneous periods
A. B.	22	0	Second- ary	30 u.	5	3	3	Treatment in progress
A. D.	24	0	Pri- mary	30 u.	10	1	0	
R. J.	30	0	Pri- mary	30 u.	15	1	0	Treatment in progress

DISCUSSION

DR. S. LEON ISRAEL.—The investigations of the past decade have made available three types of gonadotropin: pituitary, chorionic, and equine. It has also become increasingly apparent that, despite these three, the physician is still in need of a gonadotropin suitable for clinical use in selected patients. The pituitary hormone is really not available in satisfactory form. The chorionic derivative is, at best and in some mysterious manner, useful in dysfunctional uterine bleeding, for, so far as the human being is concerned, it is not really a gonadotropin. The equine gonadotropin, while seemingly potent in the human female, is somewhat disappointing in clinical trials and is, moreover, a horse serum that may give rise to atopic reactions and antigonadotropic responses. We now have a preliminary report concerning the biologic potency and possible clinical value of still another type of gonadotropin.

The essayists presented convincing experimental evidence to support the contention that a startlingly effective gonadotropin results from combining minute quantities of a gonadotropic-free pituitary extract with the relatively inert chorionic gonadotropin. It is not necessary to discuss this apparent fact, a fact which the authors' tables establish. We should, however, give some pause to the possible clinical effects of this synergistic combination, the newest of the gonadotropins.

The appearance of even a *single* episode of uterine bleeding in 19 of 23 severely amenorrheic women is an accomplishment of great interest when it is evoked through the mediation of the ovaries. It would naturally be of even greater interest were the future follow-up studies to establish the existence of a normal menstrual rhythm in some of the 19 women. Even if this does not occur, it may be hoped, in view of its ovarian field of action, that further refinement of the synergic combination will yield such a desirable effect. The excellent result attained in 14 of 16 patients with dysfunctional uterine bleeding make one wonder whether or not this salutary effect is simply the result of enhancing the antibleeding power of chorionic gonadotropin, the mechanism of which is unknown. The side-effects noted on the normal menstrual cycle are certainly not in support of that viewpoint, inasmuch as chorionic gonadotropin never disturbs the menstrual rhythm. It is likely that the alteration of the cycle results from an overproduction of estrogen, the effect of which is to inhibit the function of the anterior hypophysis.

It is certainly not fair to attempt to pass judgment on the clinical merit of a potent gonadotropin but recently brought to trial and preliminarily reported to us. It is, however, pertinent to indicate that this presentation raises several important questions which embody the chemical and pharmacologic properties of the pituitary synergist, the proper dosage to employ in order to avoid overstimulation and the therapeutic future of anovular menstruation. From the data presented it appears that the combined gonadotropin is a powerful stimulator of ovulation in the human being. Will it, we may well ask, eventually be shown that this substance gives rise to multiple ovulation of *normal* character, that is, will it result in human superfecundation? Some light may be thrown on this important question by further studies on the endometrium and by assays of the sodium pregnanediol glucuronide excreted by the treated patients, for these represent criteria of ovulation and luteal function. It is also not unreasonable to hope that this synergistic gonadotropin will be subjected to rigorous clinical trials and continued study before its release to the profession at large.

given during the first half of the cycle, the menstrual flow tended to appear in from five to eight days prematurely. If, on the other hand, total doses larger than 150 synergy units were administered during the second half of the cycle, until the day of the expected flow, there was a delay of from four to five days in the appearance of the menstrual flow.

In these regularly menstruating women, as well as in some of those who were given injections of synapoidin preoperatively, the menstrual rhythm after withdrawal of treatment was not disturbed, suggesting that even overdosage does not produce lasting harmful changes in the ovaries. In fact, the intermittent administration of 900 synergy units of synapoidin in the course of three months to one of our sterile patients, not included in this report, not only corrected the tendency to delay of her periods but also resulted in conception one month after the withdrawal of treatment.

SUMMARY

In the human subject, in whom neither chorionic gonadotropin nor pituitary extracts exerts any appreciable influence on the ovaries (the latter because of lack of concentration), the combination of relatively small quantities of each produced definite stimulation and overstimulation of the ovaries in 20 of 23 patients who received the product preoperatively.

Therapeutically, the combination of chorionic gonadotropin and the anterior pituitary extract evoked one or more menstrual flows in 19 of 23 severely amenorrheic women, some of whom had not menstruated for years, despite all other forms of treatment. Only two have thus far menstruated without further treatment.

Injections of the combined extracts arrested dysfunctional uterine bleeding in 14 of 18 patients, 4 of whom were puberal girls.

Only 2 of 8 women in whom anovular menstruation was presumably the main cause of the barrenness conceived promptly. Overdosage and the presence of other etiologic factors partly explain the lack of responsiveness of this group of patients.

The increased effectiveness of chorionic gonadotropin with the addition of a pituitary extract containing very little of the gonad-stimulating hormones is variously explained as follows:

1. That it represents merely the expression of the combined physiologic activity of the two gonadotropins.
2. That chorionic gonadotropin probably converts a prohormone, supposedly present in the pituitary extract, into an active gonad-stimulating hormone.
3. That most anterior pituitary extracts contain a principle capable of converting chorionic gonadotropin into a universal gonad-stimulating substance.

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which fortunately is rarely seen in this country. Tuberculosis and anterior poliomyelitis are occasionally indirectly responsible for asymmetrical pelves, by throwing one limb out of function so that undue pressure is exerted on the good side during formative years when the bones are still soft. Other nutritional and developmental factors may well play important roles in the formation and final shape of the pelvis, but thus far it has been impossible to make such correlations. Sex-endocrine factors are undoubtedly of *great* importance in the development of the ultimate form of the pelvis, although it is not yet settled as to just when these factors exert their influence. Racial differences undoubtedly occur also, but may in part be due to nutritional and other habits typical of different races rather than to a true ethnologic factor.

This study was planned as an attempt to clarify some of these questions. It was decided first to study roentgenologically, by a modification of the Thoms' method, the pelves of children of different ages in order to determine the pelvic shape from early childhood through adolescence and to compare the incidence of the various types with the incidence in adulthood. Although valuable in indicating whether pelvic type is predetermined or develops from a common form into the varieties which are known to exist in adults, there are limitations to the significance of such data. Developmental factors can be studied satisfactorily *only* by studying individuals at different periods of their lives; e.g., yearly from an early age through adolescence. A small beginning has been made upon this phase of the problem, and it is hoped that at some time it may be possible to say definitely whether the pelvis of any one individual starts as a certain type and remains so, or changes with increasing years. This represents a long-time study and will take years to complete.

MATERIAL

The children studied were unselected except as to age and the absence of bony deformity which would interfere with the pelvic roentgenogram. The children were obtained from the pediatric wards, and in a few instances from the outpatient clinic. Most of them were suffering from a variety of conditions, none of which seemed to have a conceivable relationship to skeletal development. In other instances the children were perfectly well. Their ages varied from 4 to 15 years. In children less than 4 years old, ossification has not progressed sufficiently to permit accurate study by the x-rays. A total of 59 girls and 16 boys has been studied to date. The ages given are those attained at the last birthday.

METHOD

Three films were taken in each case to illustrate (1) the superior strait, (2) the lateral aspect of the pelvis, and (3) the subpubic angle.

1. The views of the superior strait were taken as advised by Thoms.^{1, 2} The child sits in a semi-reclining position against a back rest. Perpendiculars are then dropped to the table from the lumbar interspace 4-5 and the symphysis. The perpendiculars are measured and the points at which they meet the table are marked. After one exposure is made the patient is removed from the table. A Thoms' lead plate with 1 cm. spaced perforations is placed in the plane of the superior strait as indicated by the upper extremities of the perpendiculars mentioned above and a second exposure is made. Great care must be exercised in placing the patient squarely on the table so that a true roentgenogram of the superior strait will be obtained. A perfect picture is one in which the obturator foramina are obscured from view, showing that the superior and inferior pubic rami are directly in line. If the patient

A COMPARATIVE STUDY OF MALE AND FEMALE Pelves IN CHILDREN WITH A CONSIDERATION OF THE ETIOLOGY OF PELVIC CONFORMATION*

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IT HAS been well established by the roentgenologic studies of Thoms,^{1, 2} Caldwell and Moloy^{3, 4} and others that adult female pelves vary considerably in conformation. These authors³⁻⁶ have shown that the variations in pelvic shape are significant with respect to the mechanism of labor, and that certain types are associated with a high proportion of obstetric difficulties. Recently Thoms and Greulich⁷ have shown that adult male pelves also vary considerably in conformation. These studies have brought out clearly that the older definitions of a "normal female pelvis" and of a "normal male pelvis" do not hold in many instances. Thoms' recent study has also revealed that there are no marked differences in the pelvic inlets of men and women, but that irrespective of the particular type, the male pelvis has a smaller capacity than that of the female.

The factors which are responsible for the variations in pelvic shape have yet to be elucidated. It would be of great interest to know whether all human beings start out with pelves of essentially the same shape, which later become molded into one of several characteristic variations, or whether the differences found in adults are present in embryonic life. In 1899 Arthur Thompson⁸ published the report of a study of 8 fetal pelves, 4 of which were male and 4 female. Thompson contended that there were characteristic differences in the pelves of the two sexes. It seemed apparent from his study that the characteristics of adult male and female pelves were present in fetal life. His drawings and photographs are quite convincing, yet distortion of the fetal pelvis due to dissection and to fixation is very possible, so that it seems unwise to accept Thompson's views unreservedly, especially in view of the small number of pelves which he studied. The final form of the pelvis may well be influenced by disease, nutrition, general development, and the sex hormones. The latter may even be responsible for the final sex differences observed in adult male and female pelves.

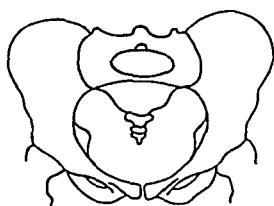
It has not been possible to establish a direct relationship between disease and pelvic conformation except in two notable instances: rickets and osteomalacia. The former produces anteroposterior shortening of the inlet and is probably responsible for the majority of the so-called platypelloid or flat pelves, a small proportion of which has been reported in every series. Osteomalacia is the cause of a marked pelvic deformity

*This study made possible by a grant from the Christine Breon Fund.

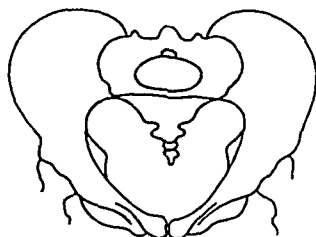
modern roentgenometric methods. Thoms' classification is somewhat different from that of Caldwell and Moloy so that direct comparison between the two is impossible. He found, however, in his study of 107 young girls, 5 to 15 years of age, that 82.2 per cent had dolichopellic (the anthropoid type of Caldwell and Moloy) pelvis. While he studied only 7 children less than 10 years of age, all but one of these had dolichopellic or anthropoid pelvis. The older the children, the smaller the proportion of anthropoid pelvis became. It would appear from our study and that of Thoms that the pelvic inlet in young girls is characteristically a long narrow oval, the anthropoid pelvis. It is not strange that basically the human female pelvis should approach in shape that of the great apes and primitive peoples. As the child approaches sexual maturity, there seems to be a tendency to anteroposterior flattening,



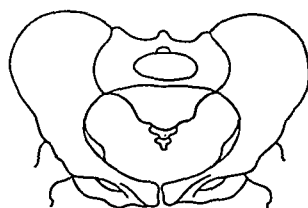
Anthropoid type



Gynecoid type



Android type



Platypelloid type

Fig. 1.—Representations of the pelvic inlet in the four main types of pelvis. For the sake of simplicity the combination types are omitted. (Adapted from Caldwell and Moloy.)

so that one finds increasing proportions of gynecoid pelvis. Whether this tendency is purely the result of sexual maturation or represents the additional influence of extraneous factors such as nutrition, disease, etc., is unknown. This tendency toward anteroposterior flattening is well illustrated by comparing the incidence of the various pelvic types in children and in adult women (Table II).

Thoms¹² made a similar comparison which illustrates the same principle in another terminology (Table III).

While the term anthropoid fits the pelvis of the youngster better than any other, there are several outstanding differences between the adult anthropoid pelvis, as described by Caldwell and Moloy,^{3, 4} and that of the child, Fig. 2. The inlet of the adult anthropoid pelvis is an oval, with the long diameter running anteroposteriorly, while that of the child does not present a smooth oval outline. In the latter instance, as the side walls of the inlet sweep forward they bend inward in the regions of the acetabula as if the lateral pelvic walls could not quite withstand the inward thrust of the femoral heads. This feature was seen uniformly in

is not squarely placed on the table the pelvic inlet will appear asymmetrical and one obturator foramen will appear more prominent than the other.

A roentgen film taken in this manner affords one the opportunity to measure the diameters of the pelvic inlet as well as to study its configuration.

2. The lateral view of the pelvis is taken with the child standing against the unexposed film, so that the distances between the middle of the symphysis and the film, and between the interspace between the fourth and fifth lumbar spines and the film are equal. Great care should be taken again in lining up the patient so that the trochanters are superimposed one upon the other. A preliminary exposure is made with the patient in this position; the patient is then removed and the Thoms' lead plate placed in the plane of the midpelvis and a second exposure made.

This exposure gives a lateral view of the pelvis with the trochanters superimposed. The centimeter dots are in scale with the midpelvis so that a definite check of the anteroposterior diameter of the inlet can be made by mensuration. It is also possible to study the lateral bore of the pelvis, the width of the greater sciatic notch, the configuration of the sacrum, and the size and shape of the ischial spines.

Because of lack of understanding and lack of cooperation on the part of the younger children studied, it was necessary to take some of the lateral views with the children lying on the table on their sides. Precautions similar to those employed for the standing position were taken to place the lead plate in the midpelvic plane. Maintenance of the correct position on the table was facilitated by placing sandbag supports at suitable points.

3. The subpubic angle was filmed according to the method advised by Pettit and others.⁹ The patient lies on her back on the table. The x-ray tube is aimed at the pelvic outlet by tilting it to an angle of 30 degrees. The resultant picture permits measurement of the subpubic angle by a geometric protractor and gives an idea of the splay of the side walls of the pelvis.

RESULTS

It was impossible to obtain perfect pictures in many instances, particularly among the younger children, but the majority of the pictures were satisfactory for the determination of pelvic type. The diagnoses of pelvic types were based upon the definitions set down by Caldwell and Moloy,^{3, 4} with special reference to the shape of the pelvic inlet. There were, however, certain variations seen in the pelves of the younger children which will be commented upon later. Caldwell and Moloy have constructed a diagram, of which Fig. 1 is a copy, which illustrates clearly and succinctly the types into which they have divided pelves. While only the characteristic inlets are represented in the diagram, their classification is based upon a consideration of other features also, such as the width of the sacrosciatic notch, the subpubic angle, the splay and bore of the pelvis, etc. These features have likewise been noted in this study. In addition many different diameters have been measured. The points of interest which have come out of these notations will be commented upon in the appropriate places.

The results which were obtained in the 59 girls are given in Table I.

Of the entire number of 59 girls, 42, or 71.2 per cent, had anthropoid pelves, and in 10 others the pelves exhibited anthropoid tendencies although they could not be called pure types. In 6 cases the pelvic inlet was gynecoid in configuration. Three of these 6 children were older girls, 14 and 15 years of age. Of great interest is the fact that in 36 of the 37 girls 11 years old or younger, the pelves were either purely anthropoid in shape or exhibited marked anthropoid tendencies. (See footnote to Table I.)

A similar finding has been recorded by Greulich and Thoms,¹⁰ who as far as we are aware, are the only other observers who have studied the pelves of children by

the pelvis of the children who were still in their pre-puberty years. On the whole, the posterior half of the child's pelvis has almost a gynecoid configuration, while the anterior half is distinctly anthropoid. This was noted particularly in the younger children, 5 and 6 years of age. In several of these, while the greatest transverse diameter of the inlet actually exceeded the anteroposterior diameter, the general conformation was that described above, and suggested immediately the anthropoid type. However, this group has been classified as gynecoid-anthropoid in order to conform as closely as possible to the classification of Caldwell and Moley.



Fig. 2.—The pictures on the left represent examples of the infantile type of anthropoid pelvis. The upper one is from an 11-year-old girl, 4 feet 5 inches tall. The lower one is from a 7-year-old girl, 4 feet 2 inches tall. The inward bowing in the acetabular regions is striking. The pictures on the right represent the adult type of anthropoid pelvis. The upper one is from a 12-year-old girl, 4 feet 10 inches tall, whose pelvic measurements are almost adult. The lower one is from a 15-year-old girl, 5 feet 5 inches tall.

TABLE I

AGE	ANTHROPOID	GYNECOID- ANTHROPOID	ANTHROPOID- GYNECOID	GYNECOID	ANDROID- ANTHROPOID
5 and less	5	4*			
6	2				
7	4				
8	6				
9	3				
10	3				
11	9			1	
12	5	1		1	
13		2		1	1
14	1		2	1	
15	4		1	2	
Total	42	7	3	6	1
Percentages	71.2	11.8	5.1	10.2	

*These four pelves looked exactly like the five classified as anthropoid in this age group, but are classified here because the transverse diameter of the inlet was slightly greater than the anteroposterior diameter of the inlet.

TABLE II

TYPES OF PELVIS	CHILDREN 5-15 59 CASES (PER CENT)	U. C. SERVICE 410 CASES HAYDEN ¹¹ (PER CENT)	CALDWELL MOLOY ⁴ 215 CASES (PER CENT)	PETTIT AND OTHERS ⁹ 100 CASES (PER CENT)
Gynecoid	10.2	54.0	39.5	51
Gynecoid-android		9.0	11.1	
Gynecoid-anthropoid	11.8	6.0	4.6	
Android		2.0	11.6	21
Android-gynecoid		2.0	5.1	
Android-anthropoid		0.7	3.7	
Anthropoid	71.2	16.0	11.6	18
Anthropoid-gyne- coid	5.1	2.0	6.5	
Platypelloid		4.2	6.0	5
Asymmetrical		2.0		5

TABLE III

TYPE	104 STUDENT NURSES	582 CLINIC WOMEN	107 CHILDREN
Dolichopellic	73 %	37.3%	82.2%
Mesatipellic	13.5%	27.5%	9.3%
Platypellic	13.5%	35.2%	8.4%

TABLE IV

AGE	ANTHROPOID	GYNECOID- ANTHROPOID	ANDROID- ANTHROPOID
5	1	1	
7	3		
8	1		
9	1		
10	1		
11	1		
12	2		
13	2		
14	2		
15			1
Total	14	1	1

In one respect only was a difference observed in the pelves of the two sexes, and as the number of observations is as yet so small one does not know how much importance to attach to this difference. The greatest transverse diameter of the inlet in the young boys was, on the average, closer to the sacrum than was that in the young girls. This fact was revealed by comparing the following quotients

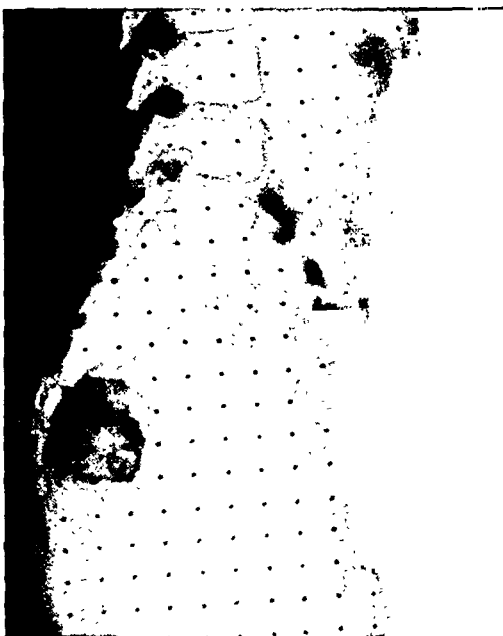


Fig. 4.—A typical case study in a 7-year-old boy. Note the similarity to the findings in the young girls as shown in Figs. 2 and 3.

in the two sexes: AP/AS , where AP represents the anteroposterior measurement of the inlet and AS represents that portion of the AP diameter lying anterior to the greatest transverse diameter of the inlet. Thus, the longer the AS , the smaller the quotient, and the closer the greatest transverse diameter to the sacrum. The average of the quotients in the 16 boys was 1.507; for the boys under 12 years of age, 1.538. The average of the quotients in 25 girls under 12 years of age was

At the present time we are engaged in studying the pelvis of pre-adolescent and adolescent boys. To date 16 boys between the ages of 5 and 15 years have been studied. The results are given in Table IV.

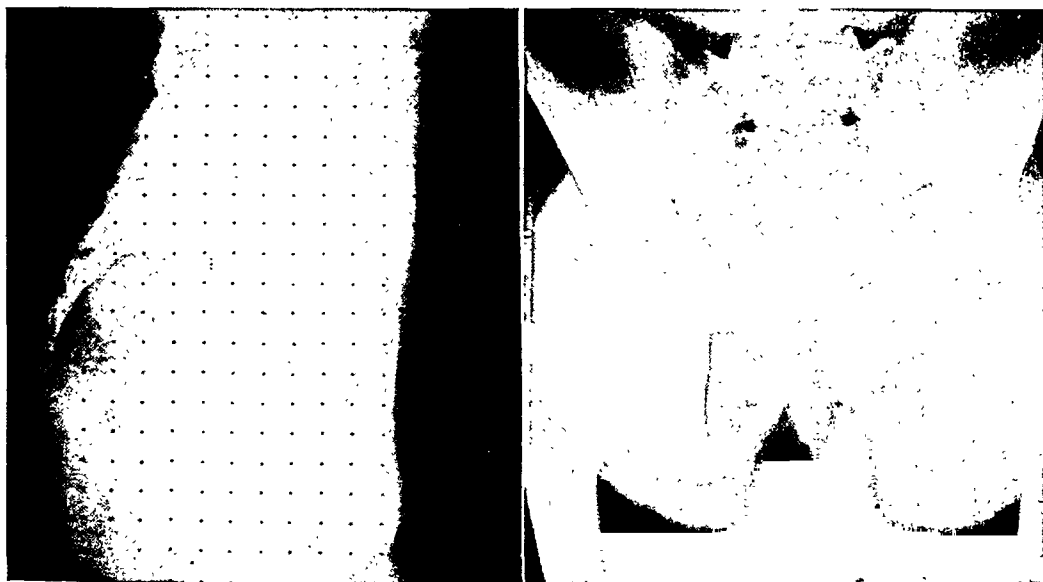
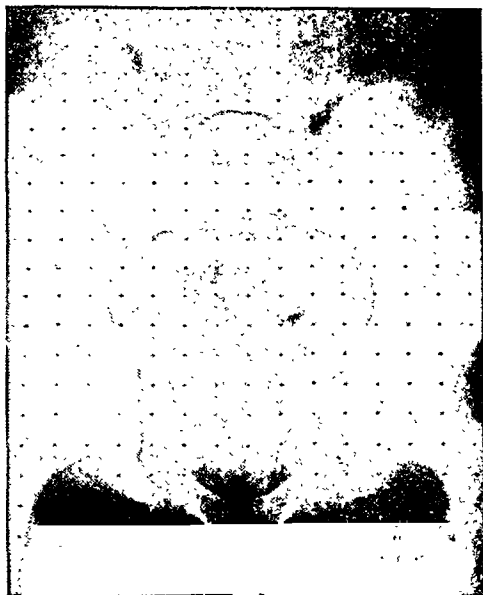


Fig. 3.—A typical case study in a 9-year-old girl, 4 feet 5 inches tall, showing the characteristic oval inlet with the inward bulge in the acetabular regions, the wide sacrosciatic notch, and the relatively high pelvis with rather narrow subpubic angle.

The pelvis uniformly were of the anthropoid type similar to that described for the girls, with the exception of one in a boy 15 years old in which distinct android tendencies were seen. Indeed, the pelvis of boys who were 11 years old and younger, that is, those boys in the frankly pre-puberty age group, were indistinguishable from those of the pre-pubertal girls. Not only was this true in regard to the shape of the pelvic inlet, but also with respect to the sacrosciatic notch, the subpubic angle and the general appearance of the bones.

contours to the anthropoid pelvis of adults; that the greater part of the evolution of the pelvis to its final characteristic male or female form takes place at about the time of puberty and is therefore probably due to sexual factors although there may be inherent differences in the pelves of the two sexes before puberty. Other factors than sex undoubtedly play a role because the final form of the pelvis in adult women and men we know to be quite variable. As to how these factors operate we are still in ignorance.

Although not many of the children studied had matured sexually for more than two or three years, the pelves of the children of post-puberty age exhibited definite changes from those of the younger children, and distinct differences between the two sexes were seen. In the older girls the gynecoid tendency (primarily, an anteroposterior flattening of the inlet) was much more prevalent than in the younger girls. In the older boys the pelvic inlet looked not unlike the anthropoid inlet seen in the older girls. The features which distinguished the older boys' pelves from those of the young boys and from the female pelves were the perceptibly increased heaviness of the bones, the greater height of the pelvis, and the generally narrower subpubic angle. What appeared to be even more characteristic than actual narrowness of this angle was the greater height of the symphysis pubis. This necessitated a backward displacement of the available space at the pelvic outlet. We were unable to observe any particular narrowing of the sacrosciatic notch, a feature which has been designated by many as one of the chief points of differentiation between male and female pelves. We did note, however, that the sacrum of the older boys seemed to angle downward in a way not seen in the female pelves, so that, with the comparative narrowness of the subpubic angle the male pelvis exhibited a definite narrowing and consequent diminution in capacity toward the outlet. This feature is illustrated in Fig. 6.

SUMMARY

The pelves of 59 girls and 16 boys between the ages of 5 and 15 years were studied roentgenologically by a modification of the Thoms' method.

In 42 (71.2 per cent) of the girls and in all of the boys, the pelvic inlet was anthropoid or dolichopellic in type. In 10 other girls, while the pelves were not of the pure anthropoid type, marked anthropoid characteristics were observable.

In all except one of the children of pre-puberty age (11 years or less), both girls and boys, the pelvic inlet was essentially anthropoid in type. Uniformly these inlets exhibited an inward bulge in the regions of the acetabula.

The pelves of the prepubertal children were indistinguishable with respect to sex, except for a possible difference in the position of the greatest transverse diameter of the inlet.

In the children of post-pubertal age, there were definite developments in the pelves which distinguished them from those of the younger children; there were also marked differences between the pelves of the two sexes.

1.610, a considerably larger figure. Thompson observed that such a difference existed between the two sexes in the fetal pelves which he studied. Furthermore, adult male pelves characteristically differ from adult female pelves in having smaller posterior segments at the inlet. Hence, while on the films the pelves of the young boys and girls appear identical, measurement reveals a possible characteristic difference, present early in life, before the changes of puberty.

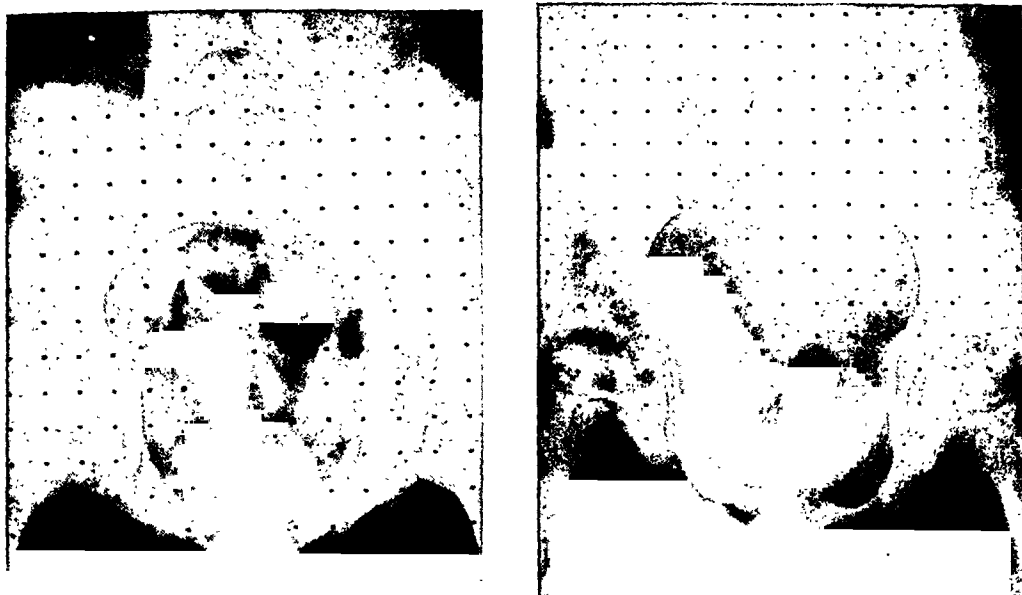


Fig. 5.—Left: Pelvic inlet of a boy 11 years old. Right: Pelvic inlet of a boy 10 years old. Note the marked similarity to the inlet of young girls as illustrated in Figs. 2 and 3.

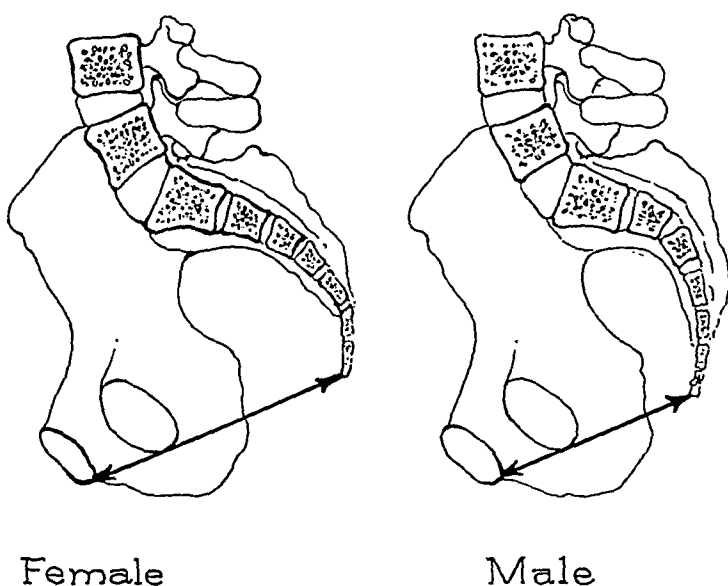


Fig. 6.

DISCUSSION

While the small number of individuals studied does not justify sweeping conclusions, the findings suggest that all human beings, male or female, are born with pelves which are most nearly comparable in their

comprising 48 women with ovarian failure reported that "in no case was there any definite evidence of stimulation of ovulation by equine gonadotropic hormone."

Reports from our clinic⁵ were among the first to call attention to the fact that chorionic gonadotropins were not true ovarian stimulators. With this experience as a background, we have been cautious to avoid any uncritical enthusiasm regarding the equine gonadotropins.⁶ We have questioned repeatedly the likelihood of the majority of patients with ovarian failure responding to gonadotropic substances, regardless how pharmacologically effective they were, since no proof had been submitted that the genesis of most ovarian failure is due to primary pituitary failure. In instances, wherein ovarian failure results from inadequate pituitary stimuli, the administration of potent and qualitatively ample gonadotropic extracts may permit successful complementary circumvention, at least temporarily, of the pituitary failure.

It has been our belief that before a true and equitable evaluation of gonadotropic therapy is possible, our knowledge of functional pathology and clinical diagnosis must be expanded; we must recognize the etiologic factors, endocrine and nonendocrine, which are involved in the production of ovarian failure, and we must be able to diagnose and segregate the causative factor or factors in the individual patient who requires therapy.

Diagnostic methods at present are not sufficiently practical or conclusive to permit in many instances a clear-cut differential diagnosis as to the pathogenesis of ovarian failure. While it is relatively easy to recognize hypothyroidism as a primary cause of ovarian failure, we cannot gauge the degree or character of the failure of the ovaries by the severity of the metabolic disturbance; at times the failure may be only of gametopathic character, while in other instances it may be fundamentally endocrinal.⁷ Microscopic studies of bits of endometria secured by biopsy within the first twelve to eighteen hours after the onset of flowing yield valuable diagnostic data and may permit fairly safe assumptions as to the occurrence or nonoccurrence of ovulation. Minor grades of ovarian failure cannot be recognized by these studies. The end results of ovarian failure reflected in the architecture of the endometrium yield no clues as to the cause of this failure. Data of essentially the same diagnostic import but with, perhaps, more limitations are secured from time-consuming and laborious determination of daily urinary titers of the pregnanediol-complex (one of the metabolic products of progesterone). We do not believe that quantitation of this compound permits a numerical expression of the severity of ovarian failure. Our ability to establish the level of pituitary function is extremely limited. Roentgenograms of the sella turcica done routinely supply significant data in only about 2 per cent of the patients. Estimations of gonadotropic titers in the blood and urine have proved notoriously unreliable. One of our greatest needs at present in the diagnosis of the cause of ovarian failure is an accurate and practical method for the quantitation of gonadotropic titers in the blood. This desired diagnostic aid would permit the segregation of hypopituitary ovarian failure

These findings suggest that both males and females start out life with pelvises which are identical *in type* and that the major differences observed in adult male and female pelvises do not appear until puberty and are therefore due to the influence of the sex hormones.

This study does not suggest a reason for the variations seen in the adult pelvises of either sex, but other factors than sex, such as nutrition and disease, probably play major roles.

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SOME OBSERVATIONS ON THE GYNECIC EMPLOYMENT OF EQUINE GONADOTROPINS*

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DURING the past decade alternate enthusiasm and pessimism have characterized clinical studies of gonadotropic therapy. At present, chorionic gonadotropins** have few champions among gynecologists: consensus of opinion denies their ability to induce ovulation in hypofunctioning ovaries. Pituitary gonadotropins† have not been available commercially in sufficient concentrations to warrant any significant clinical expectations. The clinical availability of equine gonadotropins,‡ a natural result of the important studies of Davis and Koff,¹ aroused considerable clinical interest. The fact that, as Davis and Koff demonstrated, these substances were capable of inducing ovulation in healthy women, i.e., those with receptive ovaries, led to enthusiastic therapeutic expectations and to a number of reports of successful treatment of women with irregularities of bleeding and sterility. Critical objective studies by Huber and Davis² and by Gray³ of the responses of women with spontaneous ovarian failure to therapy with equine gonadotropins have indicated that in some instances apparently normal ovarian responses have resulted. Erving, Sears and Rock,⁴ however, in a study

*Read by invitation at a meeting of the Chicago Gynecological Society, October 18, 1940.

**Prepared from pregnancy-urine, commercial preparations include *antuitrin-S*, *jollutein*, *APL*.

†Prepared from the pituitary glands of animals, commercial preparations include *maturity factor*, *gynatrin*.

‡Prepared from the serum of pregnant mares, commercial preparations include *antex*, *gonadogen*, *gonadin*, *anteron*.

juvenile; entire length of the uterus and cervix was 1 inch; the cervix measured approximately $\frac{3}{4}$ inch. Ovaries could not be felt. The vaginal epithelium was of immature type. Span exceeded height and lower measurement exceeded upper measurement. Basal metabolic rate was -4 per cent. Roentgenogram of the sella turcica was normal. Epiphyses of the long bones were open and the osseous age was estimated to be 14 to 15 years.

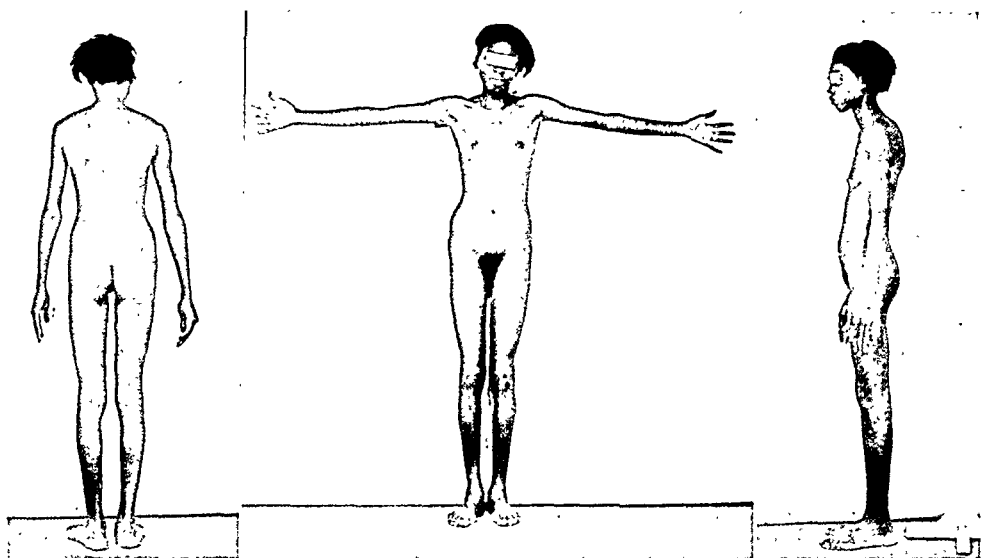


Fig. 1.—Patient 1, presenting typical statural and developmental signs of adolescent hypo-ovarianism.

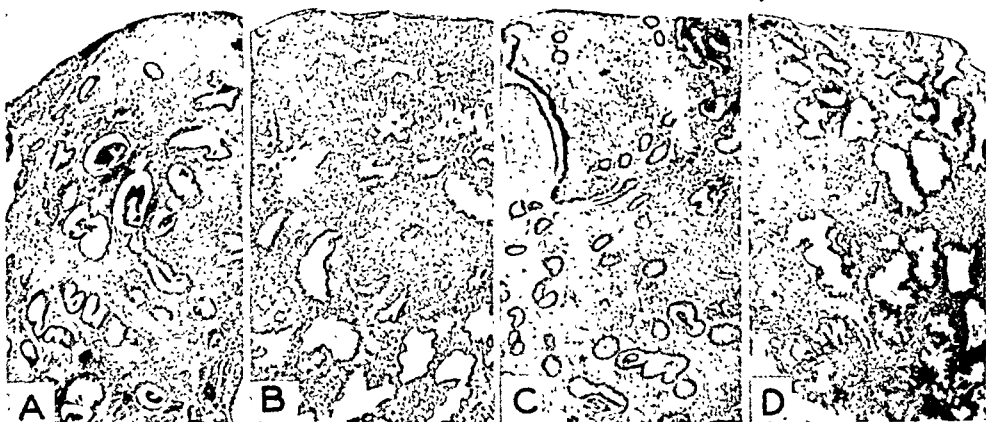


Fig. 2.—Endometrial responses of Patient 1.

The patient's treatment and her responses to it were as follows: She was given 100 R.U. of pituitary gonadotropins (maturity factor) every day for three weeks. During this therapy no significant responses occurred except a biphasic fluctuation in the leucocytes of the vaginal smears. Following this therapy she received 100 mouse units of equine gonadotropins (antex) every other day for twenty days, a total dose of 1,000 mouse units. After ten days of this treatment, a definite enlargement of the cervix and uterus was made out, and the left ovary was palpable for the first time, its size being estimated to be one-half inch in diameter. At the conclusion of this series of treatment, the ovary was thought to be cystic and to be about 1 inch in diameter. The right ovary was not felt. At the end of treatment the uterus measured 2 inches in depth and the cervix had changed from one of a flat character to a well-developed cone. A study of the biopsy of the endometrium

from those of other causes. It would seem inconsistent with rational therapy to give gonadotropins to patients having initially high gonadotropic titers in their body fluids. Such a condition (increased gonadotropic titers of body fluids) is said to occur in association with late ovarian failure of the primary and intrinsic sort and under these circumstances Watson, Smith and Kurzrok⁸ have shown that the ovaries are refractive not only to the intrinsic gonadotropins but also to large amounts from extrinsic sources.

The purpose of this communication is the presentation of some observations upon the clinical use of equine gonadotropins in the attempted treatment of ovarian failure. No intention exists of reporting a complete résumé of this experience. An attempt will be made to outline and develop certain general principles related to the clinical uses and limitations of the gonadotropins in gynecic practice.

THE TREATMENT OF ADOLESCENT HYPO-OVARIANISM

Classical adolescent hypo-ovarianism is one of the most clear-cut syndromes in endocrine gynecology. The symptoms, signs, and clinical course of patients with early ovarian failure are too well known to justify detailed description. No or minimal sexual maturation occurs. The internal and external genitalia remain infantile or juvenile in size and character. Adolescent differentiation of the breasts does not occur or progresses to a minimal degree. Menarche does not occur. The skeletal pattern is commonly a characteristic one with the span exceeding the height and the lower measurement exceeding the upper measurement. The epiphyses of the long bones remain open well past the seventeenth or eighteenth year of age and there develops frequently a characteristic statural overgrowth.

It is assumed commonly that the ovarian failure of these patients is intrinsic to the ovaries, i.e., the ovaries are regarded as being structurally incapable of responding to the tropic influences of the pituitary. The fact that these individuals often grow taller than normal women is taken to be evidence that no pituitary failure (certainly of the growth-promoting function) exists. Doubtlessly, these assumptions are true in general, but the fact that significant therapeutic results have been secured in an occasional patient who possessed all the classical symptoms and signs of this syndrome suggests that pituitary failure of the gonatropic functions may coexist with normal pituitary function as regards growth-promoting influences. A therapeutic trial of gonadotropic therapy in this syndrome is necessary, therefore, to establish the need for pituitary therapy, i.e., the presence or absence of pituitary failure (gonadotropic).

The following case is reported as an instance in which there occurred a successful response to equine gonadotropic therapy:

CASE 1.—G. R., colored, single, aged 17 years, was seen first in the Endocrine Division Oct. 13, 1937, because of delayed menarche, statural overgrowth, and sexual underdevelopment (Fig. 1). Gynecologic and endocrine surveys yielded the following data: The breasts were hypoplastic. The axillary and pubic hair were scanty. External genitalia were of juvenile type. The uterus and cervix were

metabolism tests, the results of which had ranged from -32 per cent prior to therapy to -12 per cent under thyroid therapy. Endocrine and gynecologic surveys yielded the following data: Pubic and axillary hair were scanty, having appeared at about twelve to thirteen years of age. Breasts showed preadolescent hypoplasia. There was minimal feminine padding. There was a slight hypertrophy of the clitoris, otherwise the external genitalia were small. Vagina was of normal depth, but markedly narrow in its lumen. Uterus and cervix together did not exceed 1 cm. in greatest diameter. Ovaries were not felt. Span exceeded height by 4 inches. Lower measurement exceeded upper measurement by 11 inches. Basal metabolism was -13 per cent. Roentgenogram of the skull showed the sella turcica flat, but without evidence of erosion. Roentgenogram for osseous age evaluation indicated that all the epiphyses were open, the osseous age being estimated at sixteen years. Urinary titrations for sodium pregnanediol glucuronide and for 17-ketosteroids were done on 12 consecutive twenty-four-hour specimens. There was no excretion of sodium pregnanediol glucuronide. The average daily excretion of 17-ketosteroids was 27 I.U.

Therapy was begun Oct. 12, 1939, and for the next six weeks the patient received equine gonadotropins (anteron) 400 I.U. three times weekly. A month of rest from therapy followed. Beginning Jan. 11, 1940, and for the next four weeks the patient received equine gonadotropins (anteron) 800 I.U. three times weekly. No significant clinical responses occurred. One and one-half months of rest were given. Estrogenic therapy was begun April 22, 1940. The patient was given estradiol dipropionate (di-ovocylin) 2.5 mg. (15,000 R.U.) every two days for eight weeks. Definite enlargement of the breasts resulted. Slight enlargement of the uterus and cervix was observed. Estrogenic therapy was continued in the same dosage three times a week for another six weeks. Examination on Aug. 21, 1940, indicated continued adolescent development of breasts. The uterus was definitely enlarged to about one-half adolescent size. On Aug. 23, 1940, the patient had her first episode of bleeding. Following the conclusion of this episode of bleeding, the patient was started on cyclic gonadotropins (anteron). Responses to this therapy have not been evaluated as yet.

Despite intensive gonadotropic therapy of these two patients no significant ovarian responses occurred. It may be assumed that the ovaries of these patients were refractive, that they had not failed because of a pituitary deficit, but because of structural inadequacy and that, doubtlessly, the pituitary function of both was essentially normal.

The next case is reported because the patient failed to respond to pituitary fractions and equine gonadotropins over a period of four years, and then, after intensive estrogenic therapy, gave significant ovarian responses to equine and chorionic gonadotropic therapy. The patient lacks many of the characteristic stigmas of classical adolescent hypo-ovarianism as her record will indicate. The fact that she was of dwarfish stature seemed to justify our diagnosis of adolescent hypopituitarism, but she failed to respond to pituitary therapy until after adequate estrogenic therapy had been given.

CASE 4.—Miss S. R., aged 22 years, was seen first in the Endocrine Division Aug. 24, 1936, because of delayed menarche and statural retardation. Gynecologic and endocrine surveys yielded the following findings (Fig. 3): Moderately well-developed breasts and pubic and axillary crines; slightly hypoplastic external genitalia, a small juvenile cervix and uterus, $\frac{2}{3}$ normal size; ovaries not palpable; increase in span over height of $2\frac{1}{2}$ inches. The basal metabolism was -3 per cent. Roentgenograms of the sella turcica were negative. Osseous age was estimated roentgenologically at thirteen to thirteen and one-half years. An endometrial biopsy secured hypoestrogenic (atrophic) endometrium.

The early therapeutic record of the patient was as follows: Pituitary gonadotropins (maturity factor) and posterior pituitary extract (obstetrical pituitrin)

done at the conclusion of this series of therapy indicated a good estrogenic response (Fig. 2, A). A biopsy of the endometrium was impossible before treatment because of the marked uterine hypoplasia. No bleeding followed therapy or the biopsy. No therapy was given for the subsequent four weeks. Then a second series of equine gonadotropins was given over a period of six weeks. The patient received 3,400 mouse units of equine gonadotropins (antex), the individual dose being 200 mouse units. Increase in the size of the uterus occurred during this therapy so that at the end of therapy the uterus measured $2\frac{1}{2}$ inches in depth. At the conclusion of therapy an endometrial biopsy was done, and study of the tissue obtained indicated a normal progestational endometrium (Fig. 2, B). Two days after the biopsy the first menstrual period of the patient began and lasted five days.

No further treatment was given. Twenty-six days after the onset of the patient's first period another endometrial biopsy was taken, the study of which showed a normal late estrogenic endometrium (Fig. 2, C). Fourteen days later another biopsy was taken. The endometrium secured at this time showed a good progestational response (Fig. 2, D). A menstrual period began the next day and lasted seven days. The subsequent course of the patient's bleeding was normal with cyclic menses continuing. Sexual maturation occurred rapidly. About 6 months after the patient's treatment ended, all the epiphyses were closed.

The next two cases to be presented are those of similar patients with classical adolescent hypo-ovarianism. These patients, however, failed to respond to equine gonadotropic therapy. Their dosage and its duration were far in excess of those given the first patient.

CASE 2.—Miss E. R., aged 19 years, was seen first in the Endocrine Division, July 10, 1939, because of delayed adolescence and menarche. Gynecologic and endocrine surveys yielded the following data: Axillary and pubic hair were essentially normal in amounts (having appeared four or five years previously). Breasts were of preadolescent hypoplastic nature. Feminine padding was minimum. Span exceeded height by $1\frac{1}{2}$ inches while lower measurement exceeded upper measurement by $6\frac{1}{2}$ inches. External genitalia were hypoplastic. Vagina was 10 cm. in depth. Uterus and cervix did not exceed 2 cm. in greatest dimensions. Ovaries were not palpable. Basal metabolism was -3 per cent. Roentgenogram of the skull showed the sella turcica to be normal. Osseous age estimated roentgenologically was delayed some several years, all epiphyses being open. Urinary titrations for sodium pregnanediol glucuronide and 17-ketosteroids (androgenic metabolic products) done daily for a period of fourteen days indicated the total excretion of the former during this time was 16 mg. and the average daily excretion of the latter was 18 I.U.

Therapy was initiated Aug. 3, 1939, and for the next ensuing six weeks the patient was given 200 I.U. of equine gonadotropins (gonadogen) and 300 R.U. of pituitary gonadotropins (maturity factor) every two days. No significant clinical responses were observed. A respite from therapy was allowed for six weeks. Beginning Oct. 27, 1939, and for the ensuing six weeks equine gonadotropins (anteron) were given every two days in amounts of 400 I.U. No significant clinical responses were observed. A rest period of eight weeks was given. Beginning March 11, 1940, and for the next ensuing six weeks the patient was given equine gonadotropins (anteron) in doses of 800 I.U. every two days. No evidence of ovarian stimulation was secured. On April 24, 1940, estrogenic therapy was initiated. For the next sixteen weeks the patient received estradiol dipropionate (di-ovoeylin) 2.5 mg. (15,000 R.U.) every three days. During this therapy breasts increased to the areolomammary state and the uterus to two-thirds normal size. Beginning Aug. 22, 1940, similar therapy was initiated at two-day intervals and was to be continued for six weeks following which an additional trial of equine gonadotropins was to be made.

CASE 3.—Mrs. M. B., aged 26 years, para 0-0-0, was first seen in the Endocrine Division Aug. 2, 1939, because of delayed adolescent development and failure of menarche to occur. The patient gave a history of having had repeated basal

were given in doses of 2 c.c. and 0.5 c.c., respectively, three times weekly from Aug. 28, 1936, to Sept. 30, 1936. At this time posterior pituitary extract was discontinued and the pituitary gonadotropin was continued until Dec. 14, 1936. No clinical responses were observed. From Dec. 14, 1936, to March 1, 1937, an unfractionated anterior pituitary extract (polyansyn) was given in doses of 2 c.c. three times weekly. No clinical responses occurred. From March 1, 1937, to June 9, 1938, no treatment was given the patient except small amounts of thyroid substance and estriol glucuronide (emmenin). No significant clinical responses occurred.

The remainder of the patient's therapy and ovarian responses are given in Fig. 4. During the four years of observation and treatment, the patient gained approximately 1 inch in height and 1½ pounds in weight. Epiphyseal age advanced to normal.

The striking observation in this case is that no significant responses occurred to treatment with gonadotropins until uterine growth and proliferation and cyclic bleeding had been produced by intensive cyclic sterol therapy (embracing estrogens and progesterone) and until the combined use of equine and chorionic gonadotropins was instituted. This patient's record would seem to indicate that receptivity of the ovaries to pituitary stimuli may be in some way associated with the adequacy of endometrial function. This association may be by way of the reciprocities of the ovaries and the endometrial metabolism of sterols. It certainly suggests the advisability of repeated therapeutic tests of gonadotropic therapy in patients of this type after uterine growth and endometrial priming have been obtained from sterol therapy.

No doubt exists in our minds concerning the completeness of the ovarian response of this patient since a pregnancy occurred as the immediate result of gonadotropic therapy. This was proved by an endometrial biopsy which secured chorionic villi. No bleeding followed this biopsy. No subsequent abortion occurred. It may be assumed that the product of conception was removed by the biopsy forceps. The patient has had amenorrhea from June until the present time (October). There has been no uterine enlargement indicative of continued pregnancy.

THE TREATMENT OF FUNCTIONAL UTERINE BLEEDING

We have been unable to rely upon gonadotropic therapy to regulate acyclic flowing. Even when specific ovarian responses, as judged by endometrial findings, have followed this form of treatment, cyclic bleeding frequently did not ensue and, in fact, on some occasions no bleeding occurred. We have been impelled, therefore, to employ frequently cyclic sterol therapy for the regulation of bleeding, reserving the use of gonadotropins for attempts at pregnancy in those patients in whom attendant sterility was undesired.

Ten young women, whose ages ranged from 16 to 31 years, and whose common menstrual symptom was amenorrhea, primary in 7 instances, were treated, each with one or more series of equine gonadotropins. None of these patients bled during or following therapy. No significant ovarian or endometrial alterations were observed.

Since our results with gonadotropic therapy which embraced the use of equine gonadotropins alone had not been encouraging either from

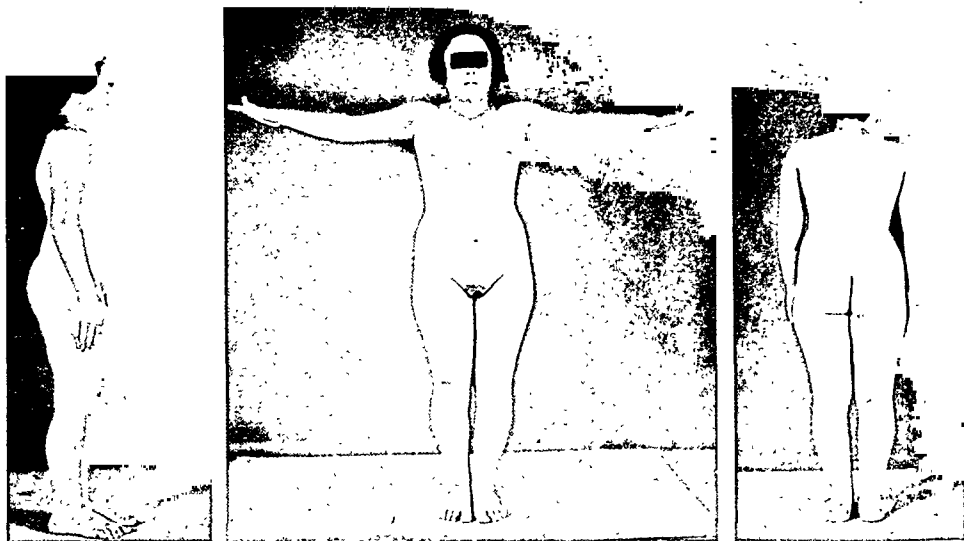


Fig. 3.—Statural and developmental status of Patient 4.

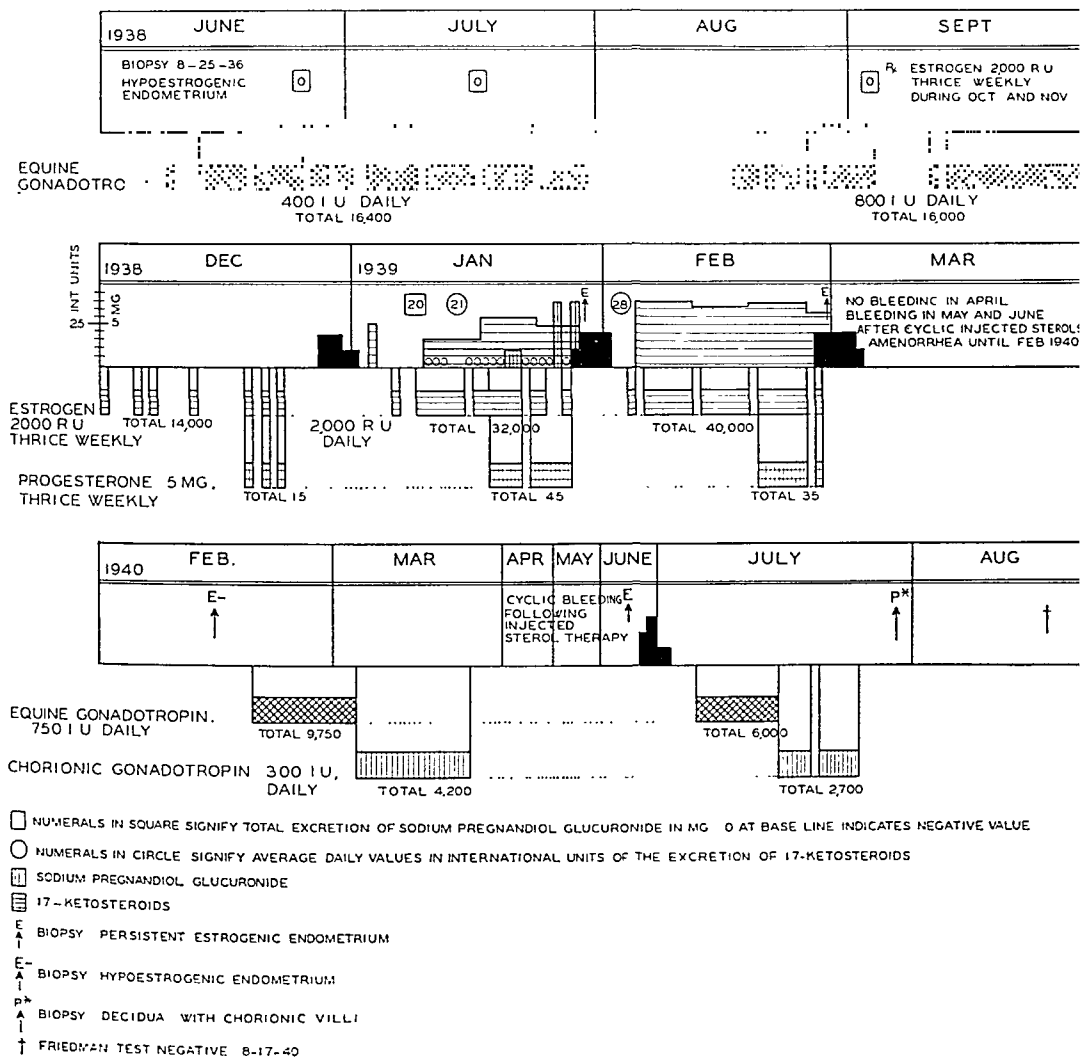


Fig. 4.—Therapeutic and progress record of Patient 4.

CASE 5.—Mrs. M. O., aged 26 years, para 0-0-0, was first seen in the Endocrine Division Oct. 24, 1939, because of metrorrhagia of eight months' duration. The patient gave a history of recurring episodes of oligomenorrhea, cyclic menses and metrorrhagia since her menarche at 13 years. Gynecologic and endocrine surveys showed nothing particularly unusual except for symmetrical obesity. Basal metabolism was +4 per cent. The menstrual irregularity was treated by curettage followed by cyclic employment of oral sterols for four months. Cyclic bleeding resulted. Biopsies of the endometrium taken at the onset of these episodes of bleeding all indicated estrogenic bleeding.

Therapy with cyclic gonadotropins was begun June 2, 1940. Fig. 5 presents graphically the details of this therapy and the endometrial responses to it.

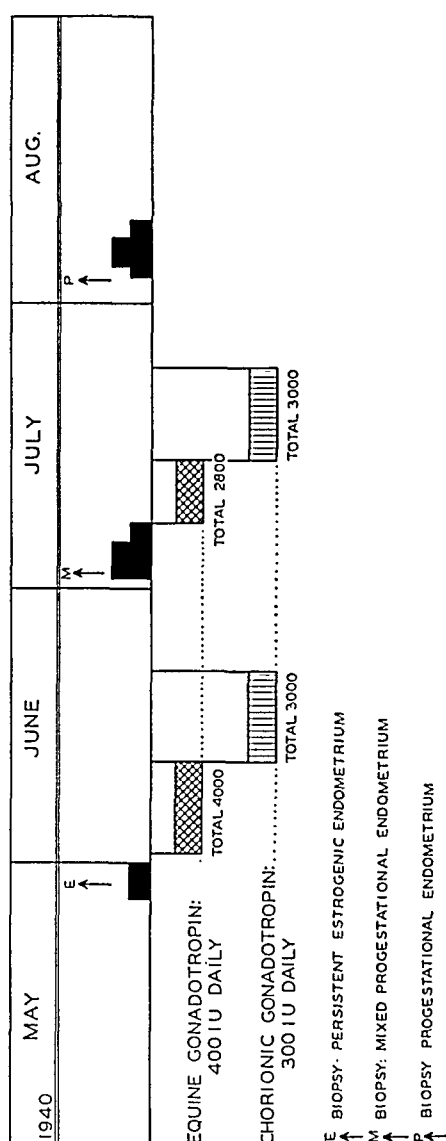


Fig. 5.—Therapeutic and progress record of Patient 5.

TREATMENT OF OVARIAN STERILITY ASSOCIATED WITH CYCLIC BLEEDING

Three women whose ages ranged from 25 to 40 years and whose symptoms included ovarian sterility and cyclic bleeding were treated with 1 or 2 series of cyclic equine gonadotropins. None of them became pregnant. One of these women illustrates the definite existence of ovarian

the point of view of subsequent ovarian responses or as judged by regulatory effects on acyclic bleeding, a system of combined therapy employing both equine and chorionic gonadotropins in one-two order was devised.⁹ In this system equine gonadotropins were administered daily during the first ten days of treatment (beginning on the fifth or sixth day of the bleeding cycle, if one existed) and chorionic gonadotropins were given daily during the last ten days of treatment. An interval of seven days following conclusion of therapy was reserved for bleeding. Following this interval another series was given, if it was deemed advisable. (The details of this form of therapy, including dosages employed, are presented in the graphic charts of Cases 4, 5, 7, and 8.)

The most satisfactory results we have secured from any form of gonadotropic therapy have followed this combined one-two system. Nineteen young women, whose ages ranged from 14 to 31 years and whose common gynecologic complaint was menometrorrhagia, related by diagnostic studies to estrogenic bleeding (failure of ovulation) were treated by this system. Five of these women responded specifically to this therapy, as judged by the induction of progestational differentiation of their endometria. It should be reported that only 2 of these 5 patients continued to bleed from progestational endometria following discontinuation of treatment. The remaining 3 experienced a return of acyclic estrogenic bleeding.

Nine young women, whose ages ranged from 25 to 36 years, and whose common gynecologic complaint was oligomenorrhea related by diagnostic studies to estrogenic bleeding, were treated similarly. Three of these women responded specifically to this therapy as judged by the occurrence of progestational differentiation of their endometria. One of these experienced a return of estrogenic bleeding of oligomenorrheic character after treatment was discontinued. One became pregnant. The follow-up record of the other one is lacking.

These data indicate that even in the small group of patients, in which positive ovarian responses follow therapy, the cure of their ovarian failure is not necessarily permanent. It is no doubt true that, when hypopituitary function is the cause of ovarian failure, continued substitution at the pituitary level is just as necessary to maintain fertile cycles as continued substitution at the ovarian level in patients with primary ovarian failure is to maintain cyclic bleeding. Continued substitution at the pituitary level with our present commercial preparations is impossible not only because of cost, but also because of antibody formation and consequent phenomena of inverse responses.

The exact *modus operandi* of this one-two system of combined gonadotropic therapy is not known. It has the support, however, of the studies on monkeys of Engle and Hamburger¹⁰ who found a similar therapeutic regime necessary for specific ovarian responses. Büttner¹¹ has had similar clinical experiences.

The following case is cited because it illustrates the fact that the cyclic employment of sterols and of gonadotropins often is necessary for the complete handling in functional menometrorrhagia.

CASE 7.—Mrs. L. R., aged 33 years, para 3-3-0, was seen first in the Endocrine Division Sept. 2, 1937. During the patient's previous five years of marriage, 3 abortions had occurred at approximately the third month of gestation. Endocrine and gynecologic surveys were essentially negative except for clinical hypothyroidism. The patient's basal metabolic reading when seen first was -21 per cent.

During a two-and-one-half-year period of study no pregnancy occurred, despite the fact that metabolic irregularities were adjusted by thyroid substance to full clinical tolerance. These studies, presented in part in Fig. 7A, indicated ovarian failure which was not overcome by thyroid therapy.

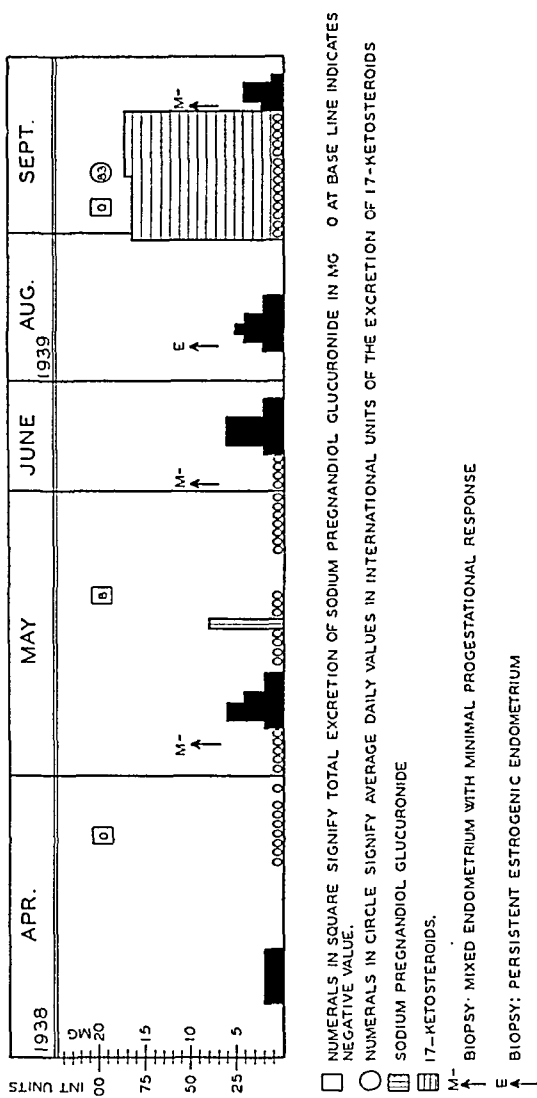


Fig. 7A.—Record of diagnostic studies of Patient 7.

On April 22, 1940, a series of combined gonadotropic therapy was instituted which led to a pregnancy. Fig. 7B presents graphically the clinical record from this time on, including therapy and urinary titrations for 17-ketosteroids and sodium pregnanediol glucuronide. This record covers the cycle preceding pregnancy, the pregnancy and the patient's spontaneous abortion July 30, 1940.

CASE 8.—Mrs. M. McC., aged 25 years, para 0-0-0, was seen in the Endocrine Division July 11, 1939, because of inability to conceive during her five and one-half years of marriage. She had had previously various diagnostic procedures, but no endocrine investigations or therapy except thyroid substance. The patient's last sterility investigation had included a tubal insufflation about two and one-half years previously.

refractivity. This is relatable doubtlessly to the climacteric process, as the patient was 40 years of age. Her case record follows:

CASE 6.—Mrs. A. G., aged 40 years, para 0-0-0, was seen first in the Endocrine Division July 5, 1939, because of her inability to conceive during her eight years of marriage, during six of which no contraception had been practiced. Endocrine and gynecologic surveys indicated no apparent cause of the patient's sterility except

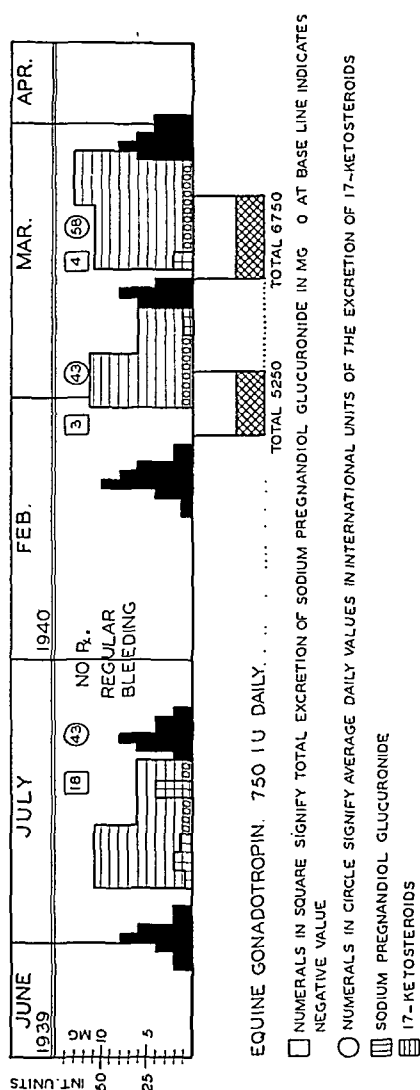


Fig. 6.—Therapeutic and progress record of Patient 6.

an acute angulation of the cervix and ovarian failure as indicated from the hormonal titrations presented graphically in Fig. 6. The acutely angulated cervix made endometrial biopsy impossible. The patient's basal metabolic rate was -1 per cent. Tubes were patent when examined by uterosalpingography with lipiodol. The husband's urologic and endocrine surveys were negative.

Two cyclic series of equine gonadotropins failed to remedy the ovarian failure as judged by urinary titers of sodium pregnanediol glucuronide (Fig. 6).

Three patients with ovarian sterility and cyclic menses were treated with combined one-two gonadotropic therapy. All 3 of these patients became pregnant promptly, in fact, during the first series of treatment. The case records of 2 of these patients are presented.

COMMENTS

We are convinced that there is a limited role in gynecic therapy for the gonadotropins. The use of gonadotropins is not the therapeutic solution to the majority of instances of ovarian failure.

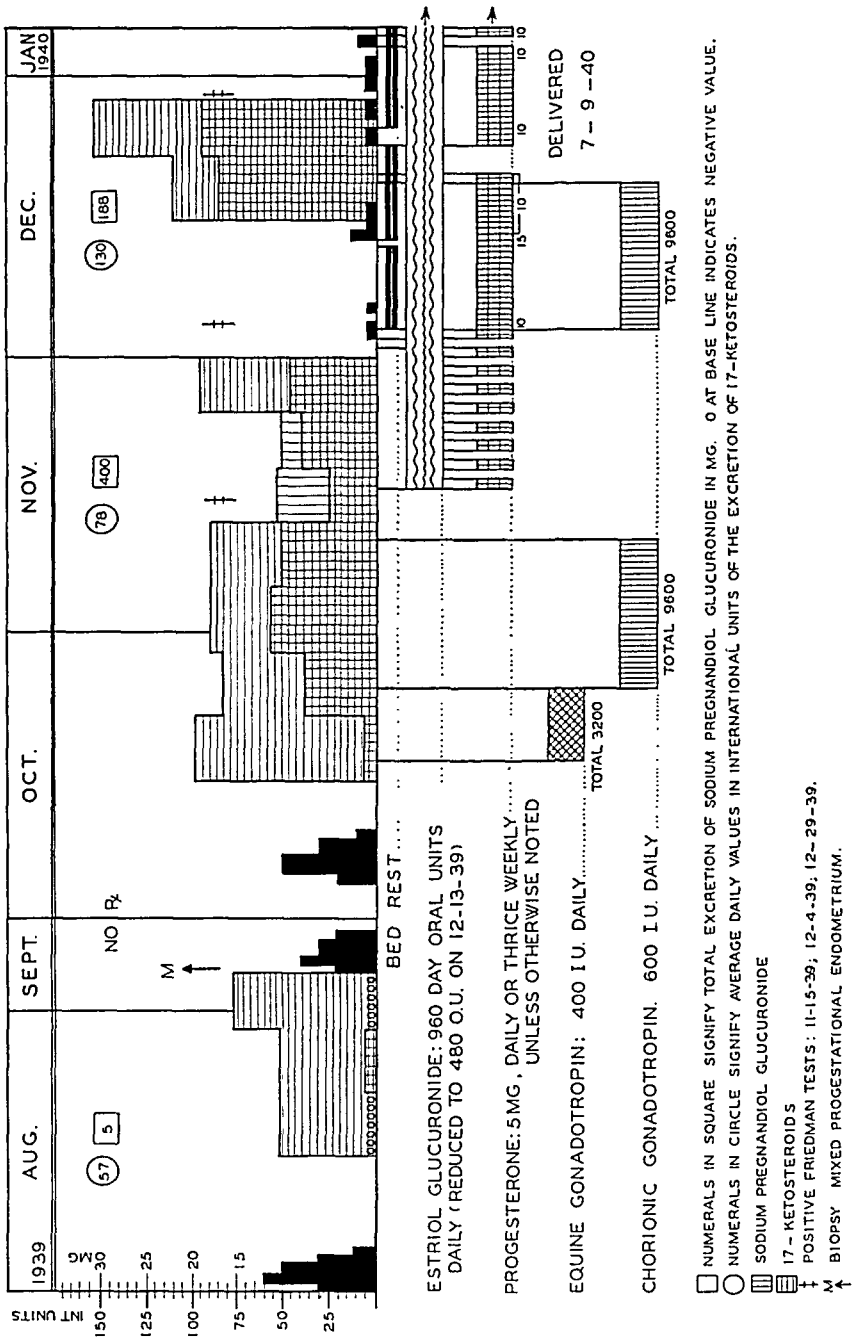


Fig. 8.—Diagnostic, therapeutic, and progress record of Patient S.

It continues to be our belief that only in those instances in which there is definite pituitary failure are these substances of any therapeutic value. Once the pituitary failure has been overcome by this therapy, the ovarian adjustment may be often only temporary. At the present time it is impossible to carry out any long time substitutional therapy

Despite the fact that the patient gave a history of marked oligomenorrhea since menarche at 15 years of age until approximately one and one-half years previously, endocrine and gynecologic surveys were essentially normal. Roentgenogram of the skull was negative. Basal metabolism was -12 per cent.

The endocrine investigation of this patient, as well as the patient's therapy which resulted in pregnancy and the course of this pregnancy, which was threatened by abortion, are given in Fig. 8.

The only special investigative procedures done by us included quantitation of urinary titers and endometrial biopsy. No tubal insufflation was done.

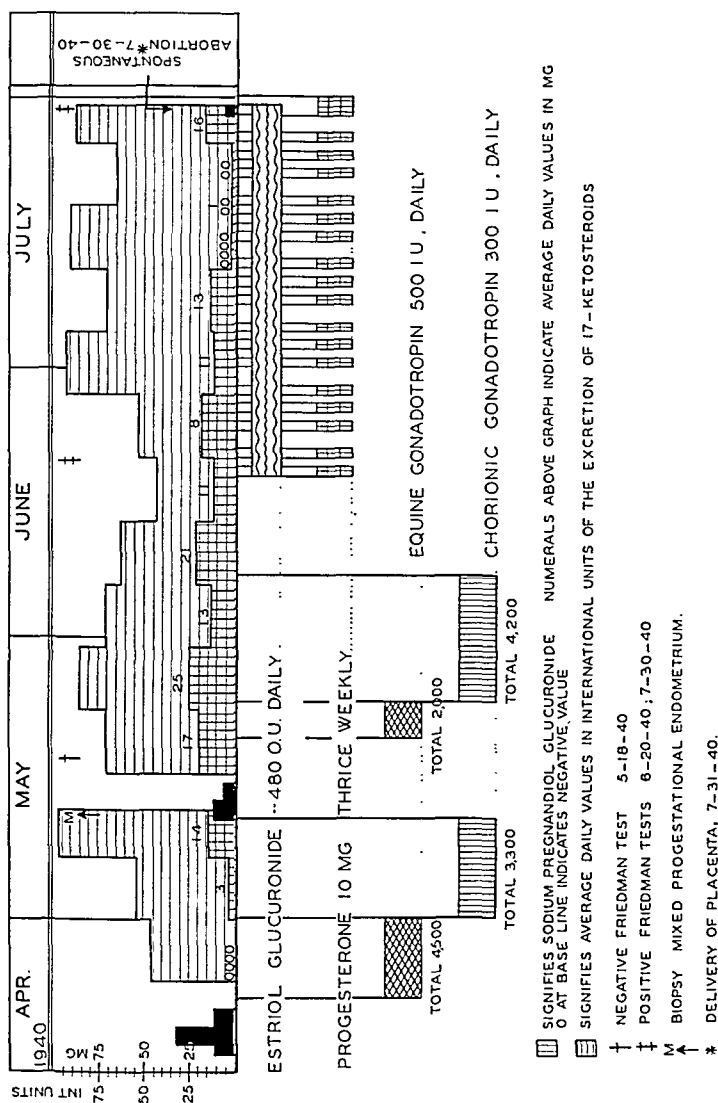


Fig. 7B.—Therapeutic and progress record of Patient 7.

It is interesting to note the obstetric history of the two patients presented: One threatened to abort; the other aborted. Abortion occurred in Patient 7 despite intensive therapy instituted at the onset of pregnancy designed to circumvent any ovarian failure during the ovarian phase of pregnancy.

These observations indicate that incurrent ovarian failure should be anticipated during early months of pregnancies in women in whom ovarian sterility was circumvented temporarily by gonadotropic therapy.

SUMMARY

1. Equine gonadotropins may stimulate ovaries which possess normal sensitivity to pituitary stimuli.
2. Equine gonadotropins are of value therapeutically in those women whose ovarian failure is due to deficient pituitary function.
3. The effects of equine gonadotropins are often temporary, the pituitary failure and the secondary ovarian failure recurring.
4. This last statement has a bearing upon the handling of pregnancy secured by this form of therapy. Intercurrent ovarian failure and abortion should be anticipated and prophylactic treatment instituted.
5. The combined one-two employment of equine and chorionic gonadotropins has proved more effective than the use of cyclic equine gonadotropic therapy alone.
6. Cyclic gonadotropic therapy in our hands fails to insure cyclic bleeding, thus indicating inadequate production of complete ovarian responses.
7. Equine gonadotropic therapy is only one of the methods available for the treatment of ovarian failure.

We acknowledge our indebtedness to the following commercial organizations for liberal quantities of specified ones of their preparations supplied for these studies: Ayerst, McKenna & Harrison, Montreal, Canada, maturity factor, polyansyn, emmenin, antex (Leo), APL; Ciba Pharmaceutical Products, Inc., Summit, New Jersey, di-ovocylin; Cutter Laboratories, Berkeley, California, Gonadin; Schering Corporation, Bloomfield, New Jersey, anteron; Upjohn Company, Kalamazoo, Michigan, gonadogen.

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DISCUSSION

DR. M. EDWARD DAVIS.—In experimental animals of a half dozen species, equine gonadotropin will substitute completely for the anterior lobe of the pituitary gland. It will produce follicle growth, luteinization and normal ovulation. Ova released from their follicles artificially can be fertilized and will develop in normal young. A major difficulty in the application to human problems is the diagnosis of the character of the glandular failure resulting in clinical manifestations, and it is therefore not surprising to find that equine gonadotropin does not always prove efficacious in medical practice.

Our experience indicates that in some adolescent and underdeveloped individuals with primary amenorrhea good results can be obtained by gonadotropic therapy. These young women mature and develop regular cyclic bleeding. In some, however, gonadotropic therapy is a complete failure. Probably in these individuals the primary amenorrhea is the result of ovarian failure, the pituitary being normal.

We have been more successful in the treatment of patients with secondary amenorrhea. In more than one-half of the individuals in this group, it has been possible to produce regular cyclic bleeding by means of equine gonadotropin. It has likewise been possible to demonstrate ovulation by endometrial biopsies in many instances.

for pituitary failure. Such therapy under favorable circumstances should be reserved for well-timed attempts to circumvent undesired sterility of hypopituitary origin.

Since it is impossible frequently to diagnose hypopituitarism, especially of a functional nature, it often becomes necessary to give patients a therapeutic test of gonadotropic therapy. This test should have finite objectives and limits. Treatment should not be prolonged indiscriminately when no responses are occurring. Likewise treatment should not be given without ample rest periods, even when responses are being obtained, for fear of antibody reactions.

Except in a few isolated instances of patients with adolescent hypo-ovarianism, our therapeutic results with the use of equine gonadotropins alone have been and continue to be extremely disappointing. The combined cyclic employment of both equine and chorionic gonadotropins in the one-two manner described by us has yielded significant specific responses in a minority group of patients with ovarian failure. These observations apparently indicate that equine gonadotropins alone are incapable of providing complete substitutional therapy in instances of hypogonadotropic failure of the pituitary. The *modus operandi* of the one-two combined therapy is not known. It may take advantage of a necessary synergism or it may afford critical alterations in sterol levels, especially those of estrogens, which are necessary for ovulation. The chorionic portion of the therapy doubtlessly tends to amplify and augment corpus luteum function, once ovulation has occurred.

Patients with classical adolescent hypo-ovarianism should be given a trial of equine gonadotropic therapy. If negative responses are given, intensive estrogenic therapy should be instituted, and from time to time the patient should be given other trials of equine gonadotropic therapy. Apparently in some instances ovarian receptivity is increased by the production of uterine and endometrial proliferation, resulting from sterol therapy. Unless complete ovarian responses can be initiated in these individuals, the establishment of complete ovarian function, compatible with fertility, is impossible.

In patients with oligomenorrhea, amenorrhea, and menometrorrhagia of functional nature, associated with undesired lowered fertility or sterility, it is often necessary to initiate and maintain cyclic bleeding with ovarian sterols while patients are being tested with cyclic gonadotropic therapy in attempts to secure pregnancies.

There is little need or rationale for the use of gonadotropins in women of climacteric age. The ovaries of these women are intrinsically refractive, and their pituitaries are either functioning normally or at higher levels than normal.

When pregnancies are salvaged from women with ovarian sterility by gonadotropic therapy, abortion or miscarriage is likely to occur from intercurrent ovarian failure. It is our opinion that each of these patients should be handled as though she gave a history of having had previous abortions.

250 to 7,000 international units. These patients were then operated upon one to five days after the last dose was given. Dr. Brewer informs me that in only one individual was there a corpus luteum present that was probably caused by the therapy.

The matter of dosage is very important. In the rat, Cole and Sanders, in 1932, noticed that with very low dose you got either no effect or slight stimulation. A high dose produces ovulation with corpora lutea. With just a little higher dose, there is apparently a rather rapid luteinization with the ovum wrapped within the corpus luteum.

During a certain season of the year in North America the monkey normally has anovulatory cycles. To 104 such animals Hartman gave equine gonadotropic hormone. Of these, 7 had a normal corpus luteum. In 32 animals there was absolutely no effect on the ovary, with just the same dose. In 16 there was a definite temporary damage to the ovary, consisting in the production of multiple large follicles which did not ovulate.

Superovulation has been produced in the rat with equine gonadotropin so that 18 to 20 young will be born instead of the 6 to 10 as normally. In the last year we have been trying to repeat these experiments and have treated 283 rats with the accepted dosage. None of our animals had over 10 offspring. This is not because we have not used potent equine gonadotropin, but no doubt because our rat colony is different from others.

These are illustrations of how important dosage is in experimental animals, but dosage is much easier to control in experimental animals than in the human being. I am wondering if some of the poor results in the human being are not due largely to the fact that the right dosage was not given. I can make no suggestion on how to decide what is the right dosage.

Dr. Hamblen presented cases which had fairly good progestational response in the endometrium and little or no pregnanediol in the urine. This brings out a point that should be mentioned. The present concept of pregnanediol is that it is very specific in a quantitative way as an indicator of the function of the corpus luteum in the human being. Dr. Hamblen's examples show that this is not necessarily true. Progesterone in its metabolism may be broken down into a good many products.

DR. HAMBLEN (closing).—A summary of our system of one-two gonadotropic therapy is as follows: On the fifth to the seventh day of the cycle (or upon conclusion of bleeding), the administration of equine gonadotropins is begun. The daily dosage has been 400 to 800 international units, given intramuscularly. Treatment continues for ten days (i.e., until the presumed time for ovulation). Immediately following the series of equine gonadotropins, chorionic gonadotropins in daily doses ranging from 500 to 750 international units are given for ten days. Therapy is discontinued if bleeding begins before the entire series has been given. If a positive endometrial response (progestational endometrium or pregnancy) follows this therapy, further treatment is not given and only is it repeated at infrequent intervals if there is a return of former pretreatment level of ovarian failure. If a negative response following therapy occurs, one more trial of it is made the next cycle.

Dr. Koff has mentioned Büttner's work (*Arch. f. Gynäk.* 163: 32, 1937) which was not referred to in my paper. Likewise, I made no reference to Engle's important study (*Endocrinology*, 18: 513, 1934; and with Hamburger, *Proc. Soc. Exper. Biol. & Med.* 32: 1531, 1935) on monkeys. Both these workers found a one-two system of gonadotropic therapy effective in inducing ovulation. Engle's observations indicated a necessity for the dual action of these two types of gonadotropins in order to induce complete ovarian responses in the monkey. (Büttner also secured ovulation from chorionic gonadotropins alone.) The explanation of the required duality of action probably lies in the necessity of "synergizing" or "augmenting" the action of equine (or follicle-stimulating hormone) gonadotropins with chorionic (or pregnancy urine) gonadotropins. Our observations lead to the belief that in the case of woman (as well as that of the monkey) equine gonadotropins do not constitute a "complete" gonadotropic principle; in women, however, with normal pituitary-ovarian reciprocities equine gonadotropins may be "synergized" or "augmented" by the pituitaries of these patients and, thereby, prove capable of inducing ovulation.

Equine and chorionic gonadotropins may well complement each other in producing a more desirable effect. The chorionic substance has little follicle-stimulating effect and consists largely of a luteinizing action. There is thus a very marked biologic difference between these two gonadotropins.

Equine gonadotropin is not a panacea for the treatment of all menstrual irregularities. There is still much to be learned concerning the proper dosage, the time interval, and the mode of administration. Until such a time as a pure principle can be isolated from the anterior lobe, equine gonadotropin appears to be the most potent gonadotrope.

DR. ARTHUR K. KOFF.—In the past Dr. Hamblén has proved to be an iconoclast with regard to the therapeutic value of gonadotropic hormones. For example, he was the first to prove conclusively that gonadotropic hormones derived from pregnancy urine have no effect on the human ovary except perhaps to produce atresia of the follicles.

Most of us who have worked with pregnant mare serum hormone fully agree with Dr. Hamblén that much more well-controlled clinical work must be done before we can prove or disprove its therapeutic value.

Experimentally the following facts with regard to the pregnant mare serum hormone have been established:

1. That both the follicle-stimulating and luteinizing gonadotropic factors are present; and consequently will produce in the ovaries of hypophysectomized laboratory animals follicle growth, ovulation, corpus luteum formation, and luteinization of mature follicles. Therefore, the pregnant mare serum hormone has the same influence on the ovary as pituitary implants or combinations of gonadotropic hormones derived from menopausal urine and pregnancy urine.

2. That the pregnant mare serum hormone is not excreted by the kidney and appears to be utilized or destroyed slowly so that a prolonged or sustained effect on the ovary occurs regardless of the route of administration.

3. That both in primates and the human intravenous administration of suitable doses of pregnant mare serum hormone will induce or hasten ovulation in the normal ovary. Theoretically then, this gonadotropic preparation should be effective particularly in those instances of hypo-ovarianism associated with pituitary failure, e.g.: amenorrhea, oligomenorrhea, and failure of ovulation. Actually in my own experience the results have been inconsistent and disappointing. For example, I have studied 21 patients with anovulatory cycles, the diagnosis having been established on the basis of repeated endometrial biopsy. To date only 3 of these patients have ovulated with pregnant mare serum hormone therapy, and I am not certain that they might have ovulated without stimulation. It is quite interesting that in this group there were 11 instances of hypothyroidism or let us say hypometabolism, with basal rates of ten or below. Eight of the eleven that showed hypometabolism began to ovulate within six weeks to three months after thyroid therapy was started. Ora Sevringhaus of New York has shown that when the thyroid is removed from laboratory animals there is a rapid disappearance of the acidophile cells of the anterior hypophyses, and it is possible that the acidophile cell is responsible for the elaboration of the luteinizing hormone. Reasoning from his observations, we can assume that a patient with decreased thyroid function probably may very well develop hypopituitarism and consequent ovarian failure.

I am very much interested in the results obtained by combining pregnant mare serum and pregnancy urine gonadotropic hormones in sequence. I remember that Büttner in 1937 described ovulation in the human female by the use of combined pituitary and pregnancy urine gonadotropic hormones explaining that the follicle-stimulating hormone prepared the follicle and the luteinizing hormone added the stimulus necessary to produce ovulation. He termed this the one-two reaction comparable to the estrogen-progestin effect on the endometrium.

DR. R. R. GREENE.—My own clinical experience with equine gonadotropin has been uniformly unsuccessful. I have secondarily observed some work being done by Dr. Brewer and Dr. Skiles. They administered to individuals with normal menstrual cycles and presumably normal ovaries doses of gonadotropic hormone, varying from

X-rays showed a questionable congenital anomaly of the kidneys, spina bifida occulta and pelvic disproportion with incomplete fusion at the symphysis pubis, following the rule that congenital anomalies are often multiple.

Urine was negative; blood count, normal; Wassermann, negative.

Operative Procedure.—On May 5, 1939, under gas-oxygen-ether anesthesia, a slightly bent-grooved director was introduced into the combined urinary and vaginal orifice with the point toward the perineum. The skin and underlying tissues which were about 3 cm. thick over the lower end of the vagina were cut in the midline down

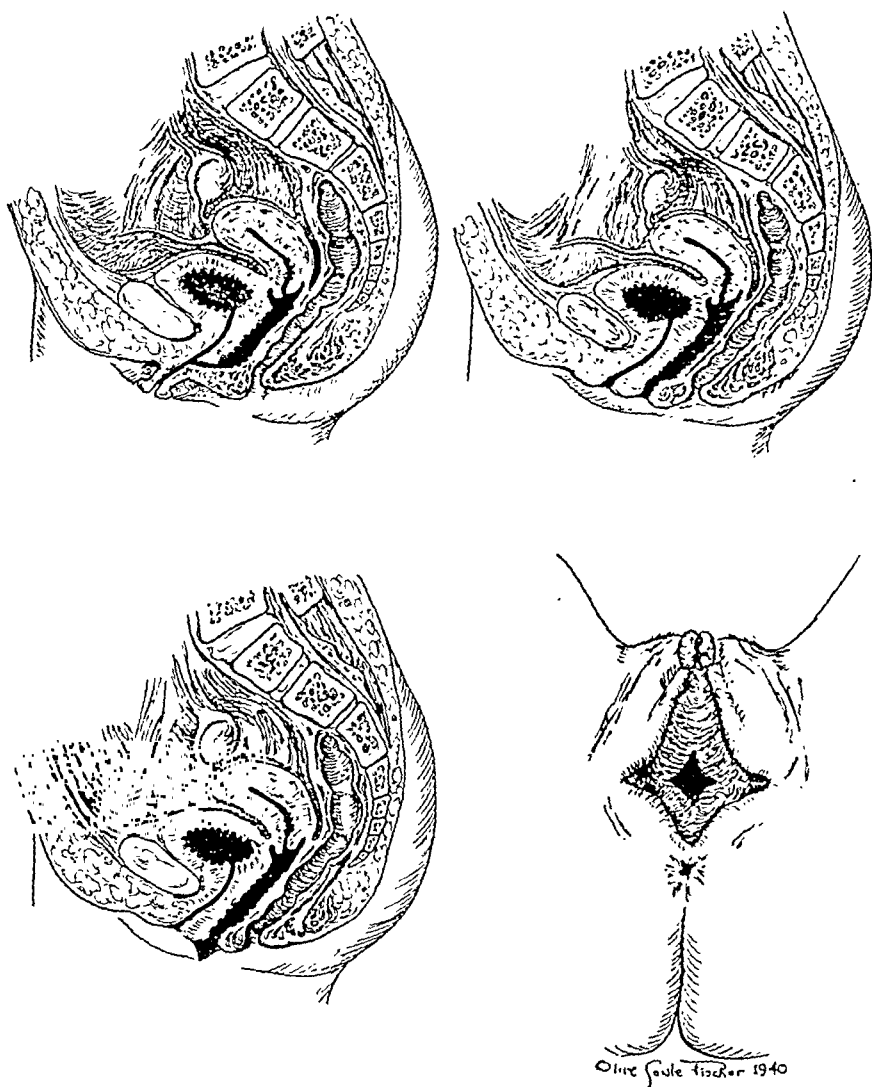


Fig. 1.

to the grooved director, thus laying open the passage and the true opening of the vagina, which admitted scant 2 fingers. This incision was extended down to the anterior border of the sphincter ani muscle. The cut vaginal mucous edges were sutured to the cut skin edges on either side with interrupted sutures of plain cat-gut. A small wick was placed in the vagina for drainage.

The patient enjoyed an uneventful convalescence and was discharged on May 11, 1939. During her stay she received the usual sedatives and urinary antiseptics to minimize an ascending urinary infection.

Patient returned to the Clinic for weekly vaginal dilatation. However, after several months it was decided that a bilateral episiotomy would accomplish dilata-

Dr. Greene has questioned if we know the effective dosage of these gonadotropins. I am sure that we do not, certainly not the minimal dosage requirements. These are conditioned, doubtlessly, by the degree of pituitary failure existing. We shall probably not be able to calculate dosage accurately until we are able to diagnose and grade pituitary failure with some degree of certainty. In some of our patients, I feel sure we have too large doses, i.e., hyperluteinized the ovaries; for instance, in those patients who yielded progestational responses but failed to bleed subsequently.

Time will not permit my answering satisfactorily Dr. Greene's question as to our opinion of the clinical significance of urinary pregnanediol. I can state only that we regard its quantitation to be a means of studying corpus luteum function, but one which does not tell the whole story and often only a small part of the story and that also we have found this study to be of little or negative value in regard to the utilization and metabolism of injected progesterone.

MENSTRUATION AND URINATION THROUGH A CLITORISLIKE STRUCTURE*

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M. B., a 21-year-old white female, was admitted to the gynecologic service on May 4, 1939, after having had a complete urologic work-up in the Urological Department. The complaints presented at this time were: (1) urination and menstruation through a penislike organ; (2) dysmenorrhea; (3) inability to have intercourse; and (4) certain psychic disturbances because of her functional deformity.

Abnormality was noted at birth, but due to the opinion of the attending doctor and the parents, nothing was done about the condition.

Menstruation began at 13 years. Periods were regular, lasting from three to four days. Periods were always painful, as were the two days prior to their onset. The menstrual flow presented itself from a clitorislike structure through which the patient normally urinated. Urine during menstruation always appeared blood tinged.

Patient had bothered little about her condition until recently, when she was made conscious of her differences from other females by the attempt of her fiance to have intercourse with her. This embarrassed her and caused her to feel very inadequate. The dysmenorrhea had recently become more severe than before.

Physical examination at the time of admission revealed a well-developed, well-nourished white female of 21 years, presenting normal secondary sex characteristics, mammary glands and hair distribution. The urethral orifice emptied from a penislike structure 3 cm. long and 1½ cm. in diameter, this urinary passage being formed by the fused labia minora, which were continuous with this clitorislike structure above. The remainder of the physical examination was essentially negative.

Cystoscopic examination revealed a normal though small vagina with an infantile cervix about 12 cm. distant from the introitus; on the anterior wall of the urinary passage about 4 cm. distant from the lower end of the true vagina the true urethra emptied. These structures were surrounded externally by skin resembling the prepuce in the male. Below was a sealed cleft surrounded by normal labia majora. The uterus was palpable rectally. The bladder was normal. Both urethral orifices were visualized, and a ureteral catheter was passed on the right and a retrograde pyelogram made.

*Presented at the New York Obstetrical Society, October 8, 1940.

AMENORRHEA AND STERILITY CAUSED BY BILATERAL POLYCYSTIC OVARIES*

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IN 1934, Stein and Leventhal described a syndrome characterized by amenorrhea and sterility associated with bilateral polycystic ovaries, and reported 7 patients treated by wedge resection. The importance of the associated findings was amplified in a recent paper by Stein and Cohen (1939) who described the subsequent course in the previously reported patients and added 22 additional cases. The following case report is a striking example of the role of bilateral polycystic ovaries in the causation of amenorrhea and sterility and adds incontrovertible evidence for the presence of this clinical entity.

CASE REPORT

Mrs. B. S., aged 26 years, consulted me on Dec. 4, 1935, complaining of amenorrhea of three years' duration and sterility of one year's duration. Menstruation began at 13 years of age and was irregular with intervals ranging from one to two months until the onset of the amenorrhea. The duration of the menses was five

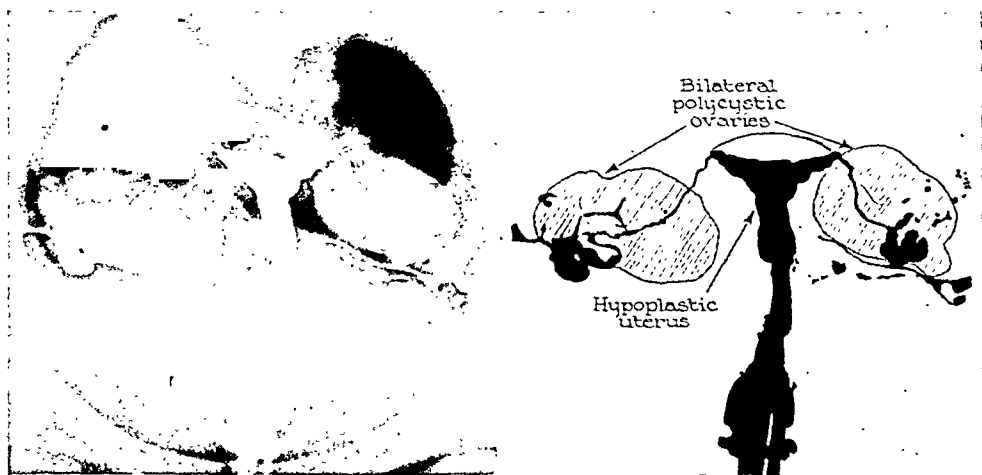


Fig. 1.—Transuterine pneumoperitoneum with lipiodol instillation. Bilateral polycystic ovaries with uterine hypoplasia. "Spill" demonstrates tubal patency.

days, the amount moderate, and there was an associated slight dysmenorrhea. There had been only one menstruation since marriage three and one-half years previously. The past history was negative, except for scarlet fever and influenza. Physical examination revealed a normal-appearing well-nourished female who weighed 135 pounds. The breasts were well developed, and there were no stigmas of masculinization. The external genitalia were normal. On bimanual examination, the uterus was found to be small, freely movable, and in second-degree retroversion. Each ovary was enlarged to a size corresponding to that of the uterine corpus, and was freely movable and nontender. On Dec. 5, 1935, transuterine pneumoroentgenography and lipiodol instillation revealed the findings indicated in Fig. 1, namely, a small uterine corpus and bilaterally enlarged ovaries. The laboratory findings were negative, and the basal metabolic rate was normal. Surgical intervention was advised, which the patient refused. She subsequently consulted six other gynecologists, and

*Presented at a meeting of the Chicago Gynecological Society, October 18, 1940.

tion of the vaginal introitus more favorably. This was done on July 20, 1939, and the patient was discharged one week later in good condition.

This case is of interest because of its infrequency; according to Engstad,¹ one in 5,000 have a similar condition.

The embryologic background of this case is interesting. In a recent article on the formation of pelvic viscera by E. Levy,² it is pointed out that the entire process of development of the external genitalia in the female is accompanied by fewer structural changes than occur in the male. Completion of development takes a longer time, so that final differentiation in the female does not synchronize with the more differentiated transformation in the male. The genital groove, however, is shorter. The groove on the tubercle becomes obliterated and the genital folds separate from the groove. Characteristic of the female is the caudal decurvation which appears to be brought about by an excess growth of the cavernous over the urethral regions of the phallus. The urethral folds develop as caudal projections supporting the slightly overhanging glans, which become more clearly defined than in the male. The caudal ends of the labioscrotal swellings grow toward each other and join in the midventral line to form the posterior commissure. In this manner these originally paired swellings are transformed into a cranially opened, horse-shoe-shaped rim, enclosing the external genitalia and separating them from the anus. The labioscrotal swellings form the labia majora. The shaft and glans of the phallus form the clitoris, and the ununited urethral folds separate from the clitoris, and become the labia minora. In the case just reported, these urethral folds united and failed to separate from the clitoris, giving the previously described deformity. Normally the unobliterated urogenital orifice becomes the urethrovaginal orifice. The prepuce is formed as in the male, but its growth is slower and generally less marked than in this instance.

The menstrual function has been normal since leaving the hospital and coitus satisfactory. Examination August, 1940, revealed ample two-finger plus introitus with ample vagina.

In summary, a case of anomalous development of the female external genitalia is presented, the indications for operation given, the operative procedure employed described, and a brief summary of the embryologic background given.

Undoubtedly this deformity arose from imperfect canalization of the lower end of the Müllerian ducts, as the layer of tissues overlying the lower end of the true vagina, showed a thickness up to 3 cm., much more than would be explained by a simple imperforate hymen. The other congenital abnormalities indicate that it was a major rather than a minor deviation in such as is frequently reported as adherent labia minora.

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130 EAST 56TH STREET

McSweeney, D. J., and Moloney, A. M.: *X-ray Pelvimetry for General Use*, New England J. Med. 223: 1043, 1940.

Experience at the Boston City Hospital during the last three years has convinced the writers that a technique, based on the method of Ball of Columbia University, is simple, inexpensive, informative, and practicable for general use.

X-ray pelvimetry should not supplant external and internal measurements and palpation, but should supplement them in questionable cases.

HUGO EHRENFEST.

Clinically, the condition may closely simulate advanced pelvic malignancy with peritoneal, and pleural or pulmonary metastases. Cachexia is not uncommon. The patient usually has known of the presence of an abdominal mass for a long time prior to consulting a physician. The ascitic fluid may be so marked that the patient is incapacitated, and the abdominal mass obscured by the distended abdomen. Attention is called to the co-existing hydrothorax by dyspnea which may have been present for months. Sufficient fluid is usually present to give ample physical findings. The diagnosis of Meigs' syndrome is relatively simple if the condition is considered.

The rarity of this condition has prompted us to report a case which has recently come under our observation, and in which the diagnosis was made pre-operatively.

V. V., aged 31 years, colored, was admitted to the Charity Hospital March 31, 1940, complaining that her stomach was swollen. Two weeks prior to admission, she began to have generalized cramping pains in her abdomen, which became progressively worse during an interval of approximately six hours. The pains subsided somewhat, and she noticed that her abdomen had become greatly distended. She had no nausea or vomiting. She ate dinner as usual, but the ingestion of food caused a recurrence of the pains. There was little or no increase in the size of the patient's abdomen from the acute onset until admission to the hospital. She had more or less constant cramping pains of varying intensity during the two-week interval. Her bowel function had been unchanged, and no nausea or vomiting occurred at any time.

She had noticed a lumpy mass in the lower abdomen for a year. She had dyspnea on climbing steps for the year prior to admission, which had become progressively more severe and was noticeable on slight exertion during the past month. Occasional palpitation was present, associated with the periods of dyspnea.

She was not confined to bed during the two weeks of her illness, but experienced discomfort on walking. She had no swelling of her feet, ankles, or hands.

The patient had a slight productive cough for one month. There were no hemoptysis, night sweats or chest pain.

Menstrual and Marital History.—The patient reached menarche at 12 years of age. Her periods occurred at a twenty-eight-day interval, lasting five to six days throughout her menstrual life. There was no dysmenorrhea. Her last menstrual period began Feb. 17, 1940. The present menstrual period began March 12, 1940. One pregnancy occurred terminating in a normal full-term delivery when the patient was 13 years of age.

History.—The past and family history revealed nothing of significance.

Physical Examination.—She was a slightly undernourished colored female with a tense protuberant abdomen. Flatness and impaired breath sounds were noted over the right base posterior and lateral to the level of the seventh rib. No râles were noted. Tactile fremitus were absent. No abnormalities were noted on examination of the left hemithorax. The heart was within normal limits on percussion and no auscultatory abnormalities were noted. Her blood pressure was 104/78.

Marked symmetrical enlargement of the patient's abdomen was present. The skin was tense. No enlarged veins were noted. A tympanitic percussion note was present in superior portion of abdomen. Dullness to flatness was noted in dependent portions of the abdomen. Shifting dullness and fluid waves were demonstrable. When the patient was in the supine position, a ballotable mass was present in the lower abdomen that extended up to the umbilicus. The mass was very hard and nodular on palpation. The mass shifted from one side of the abdomen to the other as the patient was turned from side to side. The liver and spleen were not palpable. No sacral edema was present.

Genital examination revealed a multiparous introitus with a slight cystocele and rectocele. Bartholin's glands were not palpable. No exudate could be expressed from Skene's glands. The cervix was normal in size and color. A healed laceration was present on the right side. The external os was slightly dilated; the cervix was a little softer than normal in consistency. The uterus was enlarged to the size of an eight weeks' pregnancy with a single fibroid palpable

received prolonged treatments with a variety of hormones including equine gonadogens, chorionic gonadotropic hormones, estrogens, and progesterones. Only one of the six advised laparotomy. Slight uterine spotting followed some of the glandular therapy. On Sept. 25, 1939, the patient returned and requested surgical treatment, having had *amenorrhea now for almost seven years and sterility for five years*. The findings on bimanual examination were the same as noted on the initial visit.

On Sept. 27, 1939, laparotomy was performed. The uterus was found to be hypoplastic, regular, firm, and freely movable. Both tubes were normal. Each ovary was enlarged symmetrically to the size of the uterine corpus. The tunica albuginea of each ovary was extremely thick and its surface studded with multiple follicle cysts. About two-thirds of each ovary were removed by wedge-shaped resection, and after puncturing the remaining visible cysts, the ovary was closed with fine catgut. Appendectomy was also performed for "mechanical" reasons. The patient left the hospital in ten days, after an uneventful convalescence. The microscopic report of the pathologist (Dr. Otto Saphir) was "multiple simple cysts and fibrosis of the ovary."

The first menstruation occurred on Oct. 21, 1939, or twenty-four days after the operation, and lasted seven days, with moderate flow. Bimanual examination after this period revealed a normal genital status. Menstruation occurred regularly every twenty-eight to thirty-one days thereafter, and the patient conceived after the period of April 25, 1940, having used no contraception for three months. At this writing (October, 1940) she is pregnant approximately thirty-two weeks.

Multiple follicle cysts, crowding the ovarian cortex and causing bilateral ovarian enlargement is not an infrequent cause of amenorrhea and sterility. These symptoms may be explained by an absence of ovulation due to the mechanical "blockade" by the multiple cysts which crowd the surface. Pneumoroentgenography has been a very important adjunct in the diagnosis of bilateral polycystic ovaries, since it is not infrequently difficult or impossible to evaluate the true size of one or both ovaries on bimanual examination. Rectal examination required in virgins rarely reveals the ovarian swellings.

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MEIGS' SYNDROME

FIBROMA OF THE OVARY WITH ASCITES AND HYDROTHORAX

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FIBROMA of the ovary associated with ascites and hydrothorax was first called to the attention of the medical profession by Meigs and Cass¹ in 1937. At that time they were able to collect 7 cases. In 1939, Meigs² brought the literature up to date with an additional 8 cases. Bomze and Kirshbaum³ have added two cases since the appearance of Meigs last publication. The importance of accurate diagnosis of this benign neoplasm is obvious when it is noted that of the 17 cases in the literature 15 patients were treated by surgical removal of the tumor and survived. One of the remaining 2 patients was not given the benefit of a laparotomy, and died as a result of the syndrome. The other reported by Bomze and Kirshbaum presented numerous complicating factors and died two days following laparotomy. These authors considered 3 possible mechanisms as the cause of death. First, the presence of a large ovarian tumor interfering with the progress of gestation and causing abortion, combined with the effects of toxemia and exploratory laparotomy. Second, acute glomerulonephritis which was observed on microscopic examination of necropsy material, and third, death as a result of an untreated Meigs' syndrome.

FULMINATING SYSTEMIC HEMOLYSIS FOLLOWING INCOMPATIBLE BLOOD TRANSFUSION

USE OF SODIUM BICARBONATE INFUSION IN THERAPEUTIC MANAGEMENT, WITH RECOVERY

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ALKALINE medication as an addition to therapeutic management of blood transfusion complications has its strong advocates since the experimental work of DeGowin on hemoglobin precipitation in acid tubular urine. In accordance with these views, a case of generalized fulminating hemolysis due to incompatible blood transfusion is being reported with the use of sodium bicarbonate intravenously as the basis of treatment. This was instituted less than two hours after hemorrhages from skin, buccal mucous membranes, gingival margins and the gastrointestinal tract were noted. That a similar condition had developed in the genitourinary tract was also revealed by bladder catheterization some hours later.

It is the consensus of opinion that among the serious complications involved in blood transfusion reactions, whether due to compatibility or incompatibility of blood, those relating to the kidneys are unusually severe. The suppression of urine in this case parallels that reported by others with the noticeable difference that it was of shorter duration. Since there has been such scant mention of alkaline medication in other published reports of blood transfusion anuria and treatment, the adoption of sodium bicarbonate here with the relatively early return of renal function merits consideration as a valuable agent therapeutically.

Another incidental fact in this case is also worthy of mention. This has to do with the surgical procedure and the subsequent choice of anesthesia. Because of persistent uterine bleeding as the result of incomplete criminal abortion, curettage was necessary. A spasm of the cervix prevented sponge forceps removal of the retained secundines, and spinal anesthesia was selected. As far as is known, this is the first instance that a spinal type of narcosis was used under such circumstances.

Mrs. E. B., aged 25 years, was admitted to the Jersey City Medical Center with a history of having attempted abortion by instrumentation self-performed. She had previously had three full-term pregnancies and four induced abortions. Prior to admission she stated that she had felt quite chilly on several occasions and noticed the passage of a number of clots from the vagina. When first seen at the hospital, her temperature was 103.8° F.; pulse, 104; respirations, 26. The red blood cell count was 2,970,000; hemoglobin, 40 per cent; white blood cell count, 9,780.

The following day she was taken to the operating room for a transfusion by the direct method. A little more than 200 c.c. of blood had been given when, without any warning, the patient went into sudden shock. Her face became cyanotic and she began to gasp for breath. Beads of perspiration appeared over her entire countenance, and she started to develop chills and shake so severely that she almost threw herself off the operating table. Complete vascular collapse occurred and the pulse was unobtainable.

The transfusion was immediately discontinued and the patient placed in Trendelenburg position and wrapped in blankets. With the transfusion needle still in situ, 2 minims of adrenalin, 1:1000 solution, were introduced into the circulation, and 200 c.c. of 5 per cent glucose in saline injected. The collapse then improved sufficiently for her to be removed to the ward. Here she was given oxygen continuously by nasal catheter and the glucose infusion was continued.

Shortly afterwards she developed fairly profuse vaginal bleeding which required packing, since any other manipulation directed toward removal of the uterine contents was considered too hazardous at this time. Numerous areas of purpura were noted about the body and bleeding had begun to develop at the gingival margins. In the meantime a recheck of the blood grouping was done, and it was discovered

on the anterosuperior surface. The fibroid was approximately 4 cm. in diameter. The uterus was anteverted and freely movable. The mass present in the lower abdomen extended into the pelvis, was freely movable, and was discrete from the uterus; it was noted on the left side. Slight fixation of the right adnexa was noted.

The extremities presented no gross abnormalities. No pitting edema was present.

Laboratory examination revealed no abnormalities.

Diagnosis.—Fibroma of the left ovary and uterine fibroids associated with ascites and hydrothorax.

X-ray examination of the chest on March 16, 1940, showed increased density in lower third of right hemithorax with slight displacement of the heart to the opposite side. *Diagnosis:* Fluid in the right pleural cavity.

Laparotomy on March 21, 1940, revealed a large solid tumor of the left ovary approximately 12 cm. in diameter. It was very hard and glary white in appearance. The surface was irregular. A long pedicle was present. Approximately four liters of clear fluid escaped from the abdomen when the peritoneum was opened. Uterine fibroids, chronic inflammatory disease of the right tube and ovary, and chronic appendicitis were also present. A total hysterectomy, bilateral salpingo-oophorectomy and appendectomy were done.

The pathologic report showed a large tumor mass of the left ovary, 14 cm. in diameter, slightly lobulated and very firm in consistency. On cut section the surface was yellowish white in color and contained a cystic portion 3 cm. in diameter. The tumor was largely covered by peritoneum and several dilated vessels were noted on its outer surface.

The uterus and cervix measured 10 by 9 by 3.5 cm. The cervix was lacerated unilaterally. The mucosa was smooth and pale yellow. A subserosal tumor mass was present which measured 3 cm. in diameter, well encapsulated, and firm in consistency. The endometrium measured 3 cm. in thickness and was pale yellow and soft in consistency. The right ovary was adherent to the tube and the fimbriated end was closed. The ovary contained a cyst filled with hemorrhagic fluid, other cysts present contained clear yellow fluid.

Final Microscopic Diagnosis.—Fibroma of the ovary, leiomyoma of the uterus, follicular cysts of the ovary, chronic salpingitis, and chronic appendicitis.

The patient's convalescence was particularly uneventful, and she left the hospital April 3, 1940. The patient was entirely free of symptoms during her convalescence.

X-ray examination of the chest on April 1, 1940, the 12th postoperative day, showed clearing of the opacity previously seen in the lower portion of the right chest.

Follow-Up Examination.—The patient was seen on Sept. 19, 1940. She had been entirely well since operation, had gained weight and had been able to resume her full duties about the household.

This patient presents the classical Meigs' syndrome. We agree with Meigs' recommendation that paracentesis, be done, if necessary, for accurate diagnosis of the pelvic mass. However, when paracentesis and thoracentesis are done, rapid reaccumulation of the fluid occurs. There is the danger of secondary infection of the affected serous cavities, which occurred in one of the reported cases. We were fortunate that the fibroma of the left ovary was readily palpable in spite of a relatively massive ascites and that the patient was not sufficiently embarrassed by the pleural transudate to require its removal.

There is little doubt that many cases of Meigs' syndrome have been overlooked in the past.

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DERMOID CYST OF THE OVARY WITH SQUAMOUS CELL CARCINOMA

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DERMOID cysts of the ovary are, as a rule, benign in character. Malignant degeneration in a dermoid cyst is infrequent. According to Lynch and Maxwell,¹ carcinoma may develop in an ovarian dermoid in three ways: (1) By direct extension from a carcinoma of an adjacent organ, or by metastasis from a more distant one. (2) By extension from a carcinoma, primary or metastatic, which has developed in the ovarian tissue not concerned with the dermoid growth. (3) By malignant degeneration of the epithelial structure of the dermoid itself. Carcinoma arising in the epithelial structure of the dermoid itself is a rather rare condition. Masson and Ochsenhirt² in a review of all cases reported up to 1929 considered only 33 to be proved cases of primary epithelioma of the epithelial elements of dermoid cysts. Some of the reported cases were rejected by them because of the too meager microscopic description of the specimens; some because of the failure on the part of the author to state definitely the origin of the carcinoma. Others were rejected because they were frankly not cases of carcinoma. To these 33 cases, Masson and Ochsenhirt added 4 more. In 1934, Counsellor and Wellbrock³ reported 3 additional cases, making a total of 7 cases out of 408 dermoid cysts surgically removed at the Mayo Clinic from 1912 to 1931, or 1.7 per cent. This figure corresponds with that arrived at by R. Meyer in a collective review of 1,268 dermoid cysts as quoted by Novak.⁴

It is because of the comparative rarity of this condition that the following case is considered worth reporting.

R. F., 38-year-old white female, was admitted to the Beth Moses Hospital Aug. 29, 1940, on the service of Dr. Aaron Hirsch, complaining of pain in the lower abdomen for the past two months, and acute urinary retention four days prior to admission. For the last two weeks pain became more severe and localized in the right lower quadrant of the abdomen. Four days ago, the patient had an attack of urinary retention which lasted for twenty-four hours and required catheterization. Patient noted that the size of her abdomen increased within the last few weeks.

Menses started at the age of 11 years, occurring every thirty-one days, lasting two days at a time without any pain. Her last menstrual period started on Aug. 23, 1940, and was normal in time and duration. Patient had one normal pregnancy ten years ago. There was no history of miscarriages or abortions.

Abdominal examination revealed the presence of a hard irregular mass arising from the pelvis, filling the entire hypogastrium and right iliac fossa. The mass was slightly movable and not tender. Vaginal examination showed a multiparous outlet. The cervix was felt high under the symphysis pubis. There was a hard irregular mass incarcerated in the pelvis and extending upward into the abdomen. The adnexa could not be palpated independently of the mass. A diagnosis of multiple fibroids of the uterus was made and an operation was advised.

Her blood pressure was 112/74. The hemoglobin was 12 Gm. per 100 c.c., red blood cells 5,000,000, white blood cells 14,300 per c.mm. of blood, with 88 per cent polymorphonuclear cells and 12 per cent lymphocytes. Blood sugar 75 mg., urea nitrogen 11 mg. per 100 c.c. of blood. Urine examination was essentially negative.

On Aug. 31, 1940, a laparotomy was performed under cyclopropane anesthesia, and the following was found: The uterus was situated anteriorly and to the left, slightly enlarged, containing two small fibroids on the fundus. Posterior to the uterus and filling the entire cul-de-sac was an ovarian cyst the size of a fetal head. It was firmly adherent to the posterior layer of the broad ligament, pelvic floor, and posterior surface of the uterus. Left adnexa was normal. A right salpingo-

that through an error the name of an incompatible donor had been sent. The patient was Type 2, Jansky, and the donor was found to be Type 3, Jansky.

It was at this point that the administration of sodium bicarbonate, within two hours after the reaction, was begun. Fifty cubic centimeters of a 2 per cent solution were used and repeated every four hours until the urine showed alkaline, once the anuria, which subsequently developed, had been overcome.

On catheterization twelve hours after the transfusion, a total of 50 c.c. of bloody urine was obtained. At this point the patient was becoming very restless, complained of lumbar pains, and showed slight puffiness of both eyelids. The bleeding of the gums was becoming more evident and the vaginal bleeding more profuse.

The following morning, since the uterine hemorrhage persisted, the patient was taken to the operating room for sterile vaginal inspection. On examination a steady stream of blood was seen to be issuing from the cervix. The fluid had no clotting tendency, and it was found necessary to dilate the cervix and remove the remainder of the conception product. The patient was given 50 mg. of novocaine in the spinal canal and the procedure quickly carried out. The entire uterine cavity was firmly packed after the removal of the retained placenta.

The need for blood replacement was evident, and she was given 500 c.c. of blood from a Type 2, Jansky, compatible donor without any reaction. About four hours later the patient had an emesis of about 100 c.c. gastric contents which were dark brown in color and gave a positive test for blood. The vaginal hemorrhage continued slight in spite of the firm packing for almost twenty-four hours and then stopped almost spontaneously.

During the next twenty-four hours, or two days following the incompatible transfusion, the urinary output was 6 c.c. On the third day, the patient vomited about 200 c.c. of fluid, still dark brown in color, and complained of weakness throughout her entire system. She could scarcely lift her head. At this stage, since there was no urinary output, she was given hot, moist packs every three hours in an effort to promote diaphoresis. Symptomatically, she also felt better after these treatments.

On the fourth day she was able to sip small amounts of tea and retain it, and she, generally, showed more interest in herself. Her first voluntarily voided urine appeared on this day. It was exactly 30 c.c. and was reddish in color. The next day she voided 182 c.c. but complained of a tired feeling. She was somewhat nauseated on taking fluids and these were discontinued. Jaundice was very marked by now, although it had begun to appear on the second day. The lumbar pains were very severe at this time. It was significant that on this day, the fifth since the introduction of the incompatible blood, the urine first showed alkaline reaction.

From then on there was daily renal excretion. The sixth day, it was 148 c.c. and increased gradually thereafter. Coincidentally with the kidney output, her symptoms showed steady improvement. Amounts of urine passed later were 450 c.c. on the tenth day; 1,475 c.c. on the eighteenth day; 2,000 c.c. on the nineteenth day; and 2,900 c.c. on the twentieth day.

The nonprotein nitrogen values reached high figures at times. On the day after the original transfusion, the nonprotein nitrogen reading was 62 mg./100 c.c. of blood. Four days later it had reached 103 and at one time was as high as 190 mg./100 c.c. of blood. The icteric index was 61 on the second day and finally came down to within normal limits within two weeks. The patient was discharged after thirty-eight days in the hospital, feeling perfect in health and presenting no complaints.

The tube was removed on the fourteenth day postoperative. The patient left the Hospital one week later in good condition.

This case is obviously one of primary epithelioma in a dermoid cyst arising from the epithelial elements of the tumor. While the condition is rare, it is well to bear the possibility of its presence in mind, especially if the tumor is adherent or gives unusual pressure symptoms. Careful microscopic study of each dermoid cyst is imperative. Prompt surgical removal of an ovarian tumor diagnosed as a dermoid cyst would seem advisable.



Fig. 2.—Photomicrograph of cyst wall, showing lining of stratified squamous epithelium.

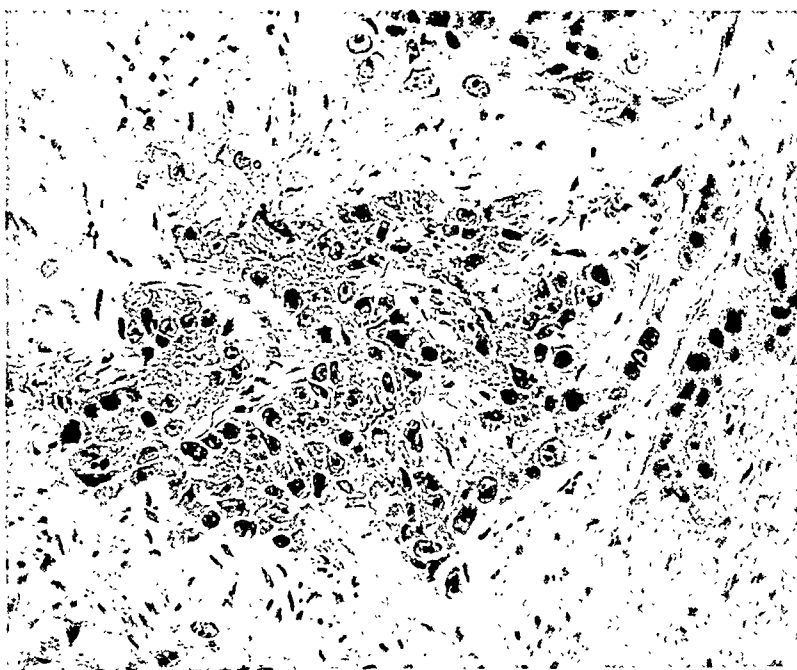


Fig. 3.—Photomicrograph showing epithelial cell nest invading thickened area; nuclei vary in size, shape, and staining capacity; mitotic figures are present.

oophorectomy was performed. The cyst was lifted out of the pelvis with great difficulty due to the dense adhesions. During this procedure the tumor was opened and found to be a dermoid cyst. The two small fibroids were enucleated.

The pathologic description of the specimen by Dr. A. Kantrowitz follows:

Gross.—Specimen consisted of two pea-sized firm, pearly-gray masses of tissue which on cross section present the characteristic appearance of fibromyomas; and a mass, the contents of which have been emptied. The measurements of the mass could no longer be determined, although it appeared to have been about the size of a grapefruit. This cystic mass was filled with hair and sebaceous material. The wall measured up to 0.2 cm. in thickness, but in one area, 7 cm. in diameter, the wall measured up to 2 cm. in thickness. In the thickened area, the wall presented a mottled grayish yellow color and a rather firm consistency. The serosa of the cyst was entirely smooth except over the thickened area, where a number of umbilicated areas were noted with considerable roughening of the serosa. A small portion of the tube, with fimbriated end, was attached to the specimen. This portion measured 3 cm. in length. Another portion of tube, measuring 4.5 cm. in length, was received separately.



Fig. 1.—Gross specimen, showing thin cyst wall with edges of the thickened area, the seat of the carcinoma, in the foreground.

Microscopic.—The cyst wall was lined by stratified squamous epithelium. The thickened area contained nests and intercommunicating strands of polyhedral, flattened cells with a clear to granular basophilic cytoplasm. The nuclei vary considerably in size, shape, and staining capacity. Mitotic figures were noted frequently. The greater portion of the thickened mass was necrotic. Areas of normal ovarian tissue were also invaded by the epithelial cell nests. The roughened surface areas were also invaded, showing nests of epithelium on the denuded areas. The inner surface of the mass showed a complete denudation of its epithelium. The tube showed no changes. The small masses consisted of smooth muscle bundles in a connective tissue stroma.

Diagnosis.—Epidermoid carcinoma in a dermoid cyst of the ovary (right); small fibromyomas.

The postoperative course was complicated by vomiting which became severe on the sixth day after operation. There was no abdominal distention. Inspection of the wound showed normal healing. A Miller-Abbott tube was passed and retained for seven days. The patient stopped vomiting, and had normal bowel movements.

Her temperature was normal. The blood count disclosed 11,850 leucocytes, 59 per cent polymorphonuclear neutrophils, 16 per cent lymphocytes, 15 per cent eosinophiles, 3 per cent monocytes, and 7 per cent stems. Examination of the stools did not disclose any evidence of parasites to account for the eosinophilia. At this time a diagnosis of herpes gestationis was made.

She was advised to take potassium permanganate tub baths, to use a drying lotion, and Fowler's solution (Liq. potass. arsenitis) was ordered in ascending doses beginning with one drop and increasing one drop daily. She reported to the dispensary each week. Fresh bullous efflorescences continued to appear even when the patient was taking seven drops of Fowler's three times a day. Fowler's solution was therefore discontinued and an effort was made to treat her with injections of serum taken from the blood of normal pregnant women. Two to 5 c.c. of the serum was injected intramuscularly twice a week for three weeks without any visible improvement in her condition.

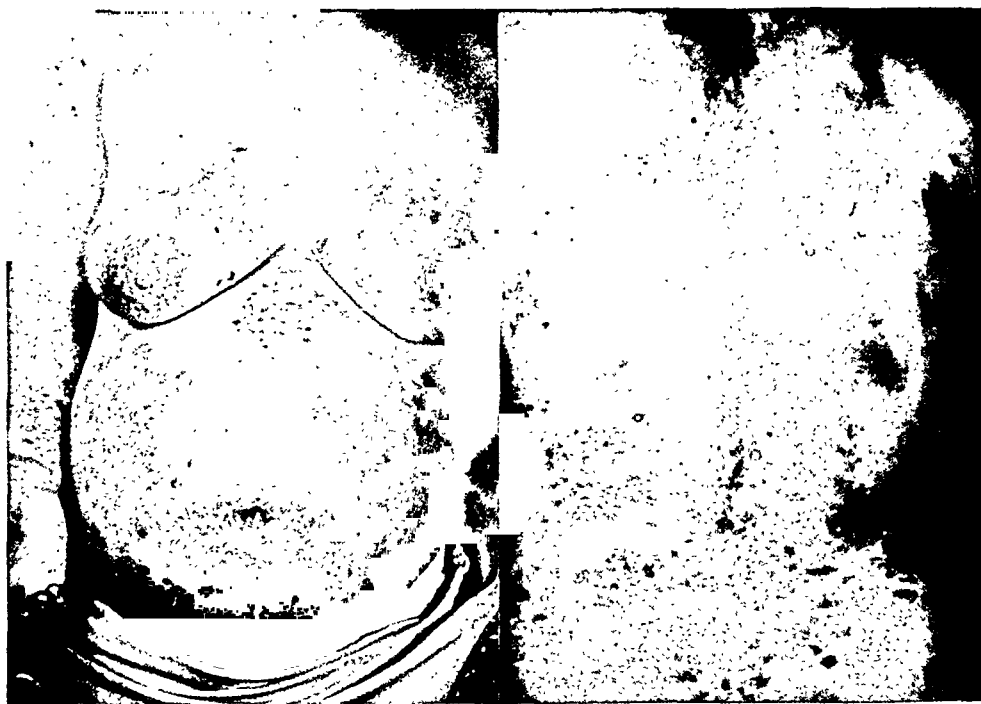


Fig. 1.—Showing the distribution of the eruption during the fifth month of pregnancy.

On Feb. 12, 1940, the patient was hospitalized. On admission to the hospital her general condition was fair. There was a slight rise of temperature. The eruption by now was generalized, covering the face, extremities, chest, back, and abdomen. The bullous type of lesion predominated. Her blood pressure was 126/70. There was no evidence of any visceral pathology. Laboratory examinations disclosed the following findings: The urine was acid and contained traces of albumin. The blood showed 4,900,000 erythrocytes, 95 per cent hemoglobin, 18,200 leucocytes, 74 per cent polymorphonuclears, 3 per cent eosinophiles, 19 per cent small lymphocytes, and 4 per cent monocytes. A gastric analysis revealed a total HCl of 40 and a combined HCl of 4. The blood chemistry findings were as follows: Sugar 69 mg., calcium 8.8, urea nitrogen 12.6, nonprotein nitrogen 24, creatinine 1.42, cholesterol 238.

It was felt that perhaps a hormone disturbance may be responsible for this disease, hence we decided to use estrogen therapy. From Feb. 12 to 18, 1940, the patient received 600,000 units of progynon B, and 70 mg. of proluton, without any influence on the eruption. Forty grains of sulfanilimide daily were tried for eleven days, and 40 gr. of sulfapyridine daily were used for six days without any amelioration of the signs or symptoms of the disease.

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HERPES GESTATIONIS

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HERPES GESTATIONIS is a rare cutaneous complication of pregnancy characterized by a multiform, vesicubullous dermatitis, marked by severe burning and itching, and affecting primarily the trunk, legs, forearms, and face. The exact etiology is unknown. It is thought by many that the cutaneous lesions result from injury to the vasomotor nerves by toxins produced by ferments from fetal tissues, or by cells from chorionic villi. It pursues a chronic course, starting usually during the latter half of gestation and ending within a few weeks after delivery. Occasionally, the condition may occur in the puerperium. It is pointed out that in these cases the eruption may result from retained placental tags. This complication tends to recur with subsequent pregnancies.

Ormsby¹ defines herpes gestationis as a variety of dermatitis herpetiformis occurring in pregnant women. According to Riecke² whose review of the subject is the most complete, Bunel³ was the first to describe this condition in 1811. Since then, this rare dermatitis was described under many terms such as pemphigus pruriginosus, herpes circinatus bullosus, dermatitis multiformis gestationis, etc. The term herpes gestationis was first used by Milton⁴ in 1872 and is at present the universally accepted term for this cutaneous complication of pregnancy.

That herpes gestationis is a rare occurrence can be seen from the statement of Irving⁵ that no patients with this dermatosis have been admitted to the Boston Lying-in Hospital during the past twenty years. Many obstetricians (personal communications) have never encountered this disease. In the past ten years only 6 case reports of herpes gestationis have appeared in the American literature.⁶⁻⁹ Hence, the report of an additional classical case is justified.

An Italian woman, aged 32, para i and gravida ii, presented herself to the prenatal clinic on Aug. 26, 1939, with a complaint of amenorrhea since June 19, 1939. Her personal and family history did not disclose any significant facts, except that her first pregnancy in 1936 was complicated by a skin eruption which appeared during her fifth month of gestation and cleared up several weeks after a spontaneous delivery at term of a seven and one-half pound living and healthy male infant.

Examination revealed that the uterus was enlarged to the size of a two months' pregnancy. Her pelvis was adequate and at this time there was no evidence of any skin or mucous membrane lesions. The heart, lungs, abdomen, ear, nose, throat, and extremities revealed no pathologic findings. There was a slight trace of albumin in the urine, a negative blood Wassermann and Kahn reaction, and a blood count within normal limits.

She returned on Nov. 18, 1939, in her fifth month of gestation complaining of attacks of intense itching and a skin rash. At this time examination revealed a discrete vesiculo-bullous eruption on her abdomen, chest, and both ankles. The eruption consisted of large patches or plaques roughly annular, clearing in the center and progressing on the periphery. As the older lesions involuted new lesions in the form of vesicles and bullae would appear. There were periods varying from a day to ten days during which time the patient was free of attacks of itching and of new lesions. There were no lesions on the mucous membranes.

where the patient only had to take three to six quarts per day. Her urinary output decreased in proportion. The patient tolerated this amount very well, but when an attempt was made to increase the dosage she developed a rather marked rhinitis. There was ever present the possibility that the posterior pituitary extract might stimulate uterine contractions and thereby cause the delivery of a premature infant.

The patient continued in this manner until April 4, 1934, when after a normal labor, she spontaneously delivered an eight-pound, living male infant.

During the first six days of her puerperium her intake remained at about six to seven quarts per day. On the seventh post-partum day, her intake abruptly dropped to one quart and has remained within normal limits ever since.

DISCUSSION

The exact etiology of diabetes insipidus is at the present time not clearly understood. It has been ascribed by some workers to be purely a deficiency in posterior pituitary lobe secretion. This is somewhat borne out by the excellent clinical results often obtained by the administration of posterior lobe extract.

Others believe that normally there is an antagonistic relationship between a diuretic hormone of the anterior pituitary, and an antidiuretic hormone of the posterior pituitary, and that occasionally this may become disrupted with a resulting relative increase in anterior lobe secretion. To support this view they offer the evidence that in the cases reported, the condition ceased abruptly in the early days of the puerperium, and this is about the time that the Aschheim-Zondek reaction became negative and signified a decrease in the amount of anterior lobe secretion.

Experimentally, it has been possible to reproduce the condition by injuries to the hypothalamus or to the nervous connection between the pituitary and the hypothalamus.

In the light of the present knowledge, it is probably more correct to look upon the condition occurring as the result of a disorder affecting the pituitary-hypothalamic mechanism and its nervous connection rather than being specifically dependent upon either the pituitary or hypothalamus alone.

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1911 WILSHIRE BOULEVARD

Madilhac, P.: Evipan as a General Anesthetic in Gynecology, *Presse méd.* 48: 252, 1940.

For anesthesia of short duration evipan is valuable as it is easily handled without danger to the patient.

As a prolonged general anesthetic evipan carries no more danger than any other general anesthetic. The author reports 1.8 per cent abnormal reactions but fails to mention the number of cases in his series. The technique is easy and utilizes minimal apparatus. Evipan induces an unusually quiet abdomen which in gynecology is an asset.

The insensible and painless induction is particularly appreciated by the nervous patients. The chief advantage of evipan over other anesthetics is the rarity of postoperative pulmonary complications following its use. The drug should be administered by an experienced anesthetist.

CLAIR E. FOLSOME.

The patients general condition became worse. There were numerous new crops of bullae, the itching was intense, and she appeared very uncomfortable and toxic. A medical induction was therefore decided upon. On March 2, 1940, at 10 A.M., twenty-four days before the calculated date of delivery, 1½ ounces of castor oil and 9 gr. of quinine were administered. Uterine contractions started several hours later, and on March 3 she delivered spontaneously a six-pound living male. On the thirteenth post-partum day she still had some bullae although new bullae ceased to appear four days post partum. Six weeks post partum all her skin lesions cleared, leaving only hyperpigmented patches. The baby was in good condition.

SUMMARY

A case of recurrent herpes gestationis, an exanthematous manifestation of a toxemia of pregnancy, is reported. Efforts to modify the course of the disease by the use of hormonal (estrogenic and corpus luteum) and chemotherapeutic (sulfanilamide and sulfapyridine) measures have failed.

We are indebted to the Schering Corporation for the supply of progynon B and proluton.

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DIABETES INSIPIDUS COMPLICATING PREGNANCY

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CASES of diabetes insipidus manifesting themselves as such only during the period of gestation and absent during the intervals between pregnancies are extremely rare. The case to be reported here is one in which the diabetes insipidus made its appearance about the sixth month of the pregnancy and ended abruptly on the seventh post-partum day. To the present time the patient has been seen at various intervals, and there is no evidence of any return of the symptoms. She has not become pregnant again due to voluntary sterility.

Mrs. H. B. C., aged 22 years, primigravida, was first seen on Sept. 23, 1933. Her last menstrual period started July 23, 1933, making her due April 30, 1934. Her past history was essentially negative as was her menstrual history.

Physical examination revealed a rather tall thin, asthenic type of female with no striking physical abnormalities. Her weight was 115½ pounds and blood pressure 110/70. Pelvic examination was negative except for the uterus which was soft, and symmetrically enlarged to about the size of a six weeks' pregnancy. The pelvis appeared to be ample.

The patient had a minimal amount of nausea, but otherwise progressed normally until the first week of her sixth month, when she noticed that she had to drink large quantities of water and was passing large amounts of urine. The patient was asked to measure her intake and output and she reported that it varied from twelve to sixteen quarts of water per day, with a corresponding output of urine.

Urinalysis at this time revealed nothing except a decrease in the specific gravity. Blood sugar, Wassermann test, and stereoroentgenograms of the sella turcica were all normal.

The patient was treated with 50 mg. of posterior pituitary powder by nasal insufflation q.i.d. This caused a rather marked reduction in symptoms to a point

1939 were caused by infection following premature or term labor and if deaths caused by infection following abortion are included we find that infection was the cause of death in slightly over two-fifths (40 per cent) of all maternal deaths.

TABLE I. COMPARISON OF PUERPERAL AND MATERNAL MORTALITY IN THE WHITE AND COLORED RACE IN NEW YORK, 1939

	TOTAL REPORTED TERMINATED PREGNANCIES	DEATHS	RATE PER 10,000 TERMINATED PREGNANCIES		
			WHITE	COLORED	TOTAL
Puerperal mortality	108,018	320	25.7	75.7	29.6
Maternal mortality	104,684	246	21.2	50.4	23.5

TABLE II. PUERPERAL MORTALITY BY CAUSE IN NEW YORK CITY. RATE PER 10,000 TOTAL BIRTHS

CAUSE OF DEATH	TOTAL	ABORTION	HEMOR- RHAGE	SEPTI- CEMIA	TOX- EMIA	ACCIDENTS OF CHILDBIRTH (INCL. CESAREAN SECTION)	ALL OTHER
INTERNATIONAL LIST NUMBER	140- 150	140- 141	144	145	146- 147	149	142 143 148 150
Average rate 1931 to 1935	54.4	10.5	6	8.2	7.8	12.6	10
Rate 1939	29.6	4.6	4	6.8	3.4	6.7	4.1
Decrease	24.8	5.9	2	1.4	4.4	5.9	5.9
Per cent decrease	45.6	56.2	33.3	17.1	56.4	46.8	59

3. The incidence of cesarean section is 2.4 per cent; the lowest rate prevails in the municipal (1.6 per cent) and the highest rate in the voluntary hospitals (3 per cent). Sixty-eight, or 2.7 per cent, of the 2,558 patients operated upon (cesarean section) died during or following the operation. The role of this operation as a cause of death would appear significant if the following facts are taken into consideration as revealed in Table III. The type of patient cared for in the different institutions obviously plays an important role.

TABLE III. CESAREAN SECTION, CITY OF NEW YORK, 1939. INCIDENCE, MORTALITY, AND PERCENTAGE OF ALL PUERPERAL DEATHS CORRELATED WITH TYPE OF INSTITUTION

	CITY AS A WHOLE	MUNICIPAL HOSPITALS	VOLUNTARY HOSPITALS	PROPRIETARY HOSPITALS
Incidence of cesarean section	2.4	1.6	3.1	1.9
Mortality in patients delivered by cesarean section	2.7	5.1	2.1	3.3
Per cent of all puerperal deaths associated with the operation	21.3	12.6	26.0	34.2

A more detailed study of important causes of death becomes necessary before constructive suggestions may be advanced. With very few exceptions something constructive should be obtained from every death. All must agree that, with the data available, it is quite improbable that any two individuals could agree entirely on the analysis relative to indication for operation, technique of procedure or other opinion that may be expressed.

Cesarean Section.—Since the inauguration of the Committee of New York County, 58 deaths associated with cesarean section have been studied and are available for analysis at this time. It is understood that some of these deaths are in

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

A STUDY OF PUERPERAL MORTALITY IN NEW YORK CITY (1937-1940) WITH ESPECIAL REFERENCE TO PREVENTIVE FACTORS*

R. GORDON DOUGLAS, M.D., NEW YORK, N. Y.

IN 1937 the New York County Medical Society appointed a Maternal Welfare Committee to study all puerperal deaths occurring in the Borough of Manhattan. Meetings open to all members and held at monthly intervals when the records of puerperal deaths are presented in detail. Anonymity of patient, doctor, and hospital is maintained. This tends to promote a more frank discussion than would be possible otherwise and greatly increases the educational aspects of the meetings.

Our knowledge concerning the statistical aspects of puerperal mortality has been fairly reliable during the present century. In general, however, the information acquired at the present time is more detailed and accurate than that previously compiled. It is to be hoped that future trends based on these comprehensive data will make more pleasant reading than some of the reports submitted in the past.

The average "puerperal mortality" rate in New York City for the first 35 years of the present century was approximately 52 per 10,000 reported terminated pregnancies. In the four years following (1936 to 1939), the rates were 44.3, 38.2, 33.4 and 29.6, respectively. Undoubtedly, then, the rate dropped rather abruptly beginning with 1936, while previous to that year there was no significant trend in either direction. There is no correlation between the birth and the puerperal mortality rates as the former has decreased progressively from approximately 36 to 14.5 per 1,000 population while the latter remained essentially the same during the thirty-five years referred to. The birth rate has been relatively stable during the past few years when the significant decrease in the puerperal rate occurred. There has been an almost comparable decrease in the puerperal mortality as revealed by our national figures so that the factors responsible for the improvement are probably largely national rather than local in scope. One can only speculate on the effect of certain known local conditions, such as, improved diet and housing made available by relief to the lower economic classes, earlier and better prenatal care to the same group, increased medical interest in and study of the problem in general, better education of medical students in the theory and practice of obstetrics, and the educational effect of the various maternal welfare groups appointed by the county medical societies, in promoting the practice of better obstetrics.

A careful interpretation of a statistical analysis by Duffield¹ of puerperal deaths occurring in New York during the year 1939 reveals the following important facts:

1. The puerperal mortality is much higher in the colored as compared to the white race, and the rate increases progressively with advancing age, irrespective of parity (Table I). The death rate in city hospitals exceeds that of voluntary hospitals by approximately two and one-half times.

2. If we compare the 1939 rate with the average of the 1931 to 1935 rates, it becomes evident that deaths ascribed to abortion, toxemia, and "all other" causes have decreased in excess of the average decrease in all causes, while the percentage of deaths associated with infection and hemorrhage has diminished relatively little (Table II). In fact, nearly one-quarter of all puerperal deaths in

*Read at a meeting of the New York Obstetrical Society, Oct. 8, 1940.

factors in 53 (91.4 per cent) of the deaths that may have modified the outcome in a considerable number of these patients. If we correlate the cause of death with the type of operation, additional information concerning some of the factors involved is revealed. The data are presented in Table VII.

TABLE VII. TYPE OF OPERATION CORRELATED WITH CAUSE OF DEATH

CAUSE OF DEATH	CLASSICAL OPERATION		LOW FLAP OPERATION		OTHER OPERATIONS*		TOTAL
	NO LABOR	LABOR (3-72 HR.)	NO LABOR	LABOR (1-60 HR.)	NO LABOR	LABOR (24-60)	
Infection	4	3		15		2	24
Hemorrhage	3		4	2		2	11
Other	4	2	5	7	1		19
Totals	11	5	9	24	1	4	

*Porro, extraperitoneal, and peritoneal exclusion. (Four insufficient data to classify.)

I regret that I cannot present the total number and type of operations done in the county during the period that the above deaths occurred. It is quite likely, however, that the incidence would not vary significantly from the figures given in Table III.

The evidence suggests that the low flap operation in the absence of labor reduces the incidence of deaths from infection, but the procedure done under these conditions, namely, with a poorly developed lower uterine segment, may be more dangerous from a point of view of hemorrhage. A low flap cesarean section done after fifteen or more hours of labor is a dangerous procedure in my belief.

Another approach to the cause of death reveals the fact that 16 of the 58 patients, approximately 27 per cent, died on the day of operation; 11 were associated with hemorrhage, 3 with the anesthesia, and 2 died from other causes.

Forty-five of the deaths occurred in 21 voluntary or proprietary hospitals and 13 in three city hospitals. This information does not appear to be particularly constructive and no further comment will be made on the subject.

The gross fetal mortality is not available because information concerning neonatal deaths is lacking. There were, however, 9 stillbirths or deadborn which represent a fetal mortality of approximately 16 per cent. If we deduct the fetal mortality associated with premature separation of the placenta and placenta previa, there still remain 6 deaths representing a fetal mortality of over 10 per cent.

After a careful study of the individual records, there appear to be obvious errors in the management of many of these patients. It is probable that many of them could not have been prevented under the circumstances of present-day practice in this city. With some changes in organization, adherence to well-defined principles and concentrated effort, the results should be modified. In Table VIII

TABLE VIII. POSSIBLE ERRORS IN MANAGEMENT OF CESAREAN SECTIONS

Duration of labor too long before operation	12
Anesthesia	11
Procrastination and delay in transfusion	9
Anemia (ante partum) (Hb. per cent was often unreported)	4
Error in technique	8
Inadequate preoperative care of cardiacs	2
Total	46

the common errors are summarized. At times more than one error has been drawn from a given case.

If something concrete can be done to eliminate such factors as have been cited, a definite decrease in the mortality in this group, which represents approximately one-fifth and one-third of the puerperal and maternal mortality, respectively, in this county, may be expected.

no way related to the procedure of delivery involved, on the other hand, certain deaths appear to have been definitely due to the operation.

The indications for operation are listed in Table IV. In many instances multiple

TABLE IV. INDICATIONS FOR CESAREAN SECTION, 58 CASES

Clinical dystocia (after trial labor)		13
Contracted pelvis		10
Clinical diagnosis	5	
X-ray diagnosis	5	
Previous cesarean section		8
Placenta previa		6
Premature separation of the placenta		2
Other		19
Heart disease	4	
Pre-eclampsia	4	
Failed forceps	1	
Myomas	3	
Abnormal presentation	2	
Uterine inertia	1	

indications make it difficult to determine the most important cause. For this and other reasons little discussion appears necessary concerning the indications, excepting to note that 8 cases (one-seventh approximately) were done primarily because of a previous cesarean section. One can realize how the initial maternal mortality associated with this operation does not tell the whole story. The pyramiding effect of maternal mortality becomes apparent where the termination of subsequent pregnancies by this means is done primarily because of the history of a former operation. In general, our experience indicates that close scrutiny of possible contraindications to operation may be equally important to a careful survey of the indications.

Anesthesia was directly responsible for three deaths. A careful study of the individual records leads me to believe that it played an important role in eight additional cases. Table V summarizes the anesthetic agents employed.

TABLE V. TYPE OF ANESTHESIA EMPLOYED IN 58 CASES OF CESAREAN SECTION

Nitrous oxide plus ether	39
Cyclopropane	5
Local	3
Other	3
Unknown	8

I believe that if 90 per cent, instead of 5 per cent, of these operations had been carried out under local anesthesia there would have been a definite reduction in the mortality. The various advantages of local over general anesthesia will be discussed later.

TABLE VI. CAUSE OF DEATH IN CESAREAN SECTION

	NUMBER	PER CENT
Infection	26	44.8
Hemorrhage and shock	11	17.2
Cardiac	5	8.6
Pneumonia	4	6.8
Toxemia	4	6.8
Anesthesia	3	5.1
Other	5	8.6

The causes of death in these patients are detailed in Table VI. A careful study of the individual cases that make up this material suggests that there are controllable

appear that deleterious effects, as a result of general anesthesia, occur much more frequently than is usually thought to be the case. For these reasons a general broadening of the indications for local anesthesia appears indicated and should include such conditions as upper respiratory infections, other medical complications, toxemias, long labors, and when delivery is to be accomplished by cesarean section.

The wider adoption of the local technique would, I believe, save lives, although certain obstetric procedures such as, version and extraction, breaking-up the frank breech, and other intrauterine manipulations, require deep surgical anesthesia.

I have discussed rather briefly in the preceding pages deaths associated with cesarean section, hemorrhage, infection, and anesthesia. I have not called attention to deaths following traumatic obstetric operative procedures in an attempt to effect delivery through the undilated cervix or to patients with antepartum bleeding who were subjected to examination or to treatment without adequate provision for therapeutic procedures or to the employment of incompatible blood for transfusion or to other ill-advised procedures. Our New York County Committee is of the opinion that improvement in obstetric practice has occurred during the past three years. The character of the discussions at our meetings has improved steadily and the inhibitions of the discussor have been largely removed.

SUMMARY

Certain facts pertaining to puerperal mortality in New York City have been presented. It appears that the rate has been decreasing steadily for the past four years while it remained essentially stationary during the preceding thirty-five years. Etiologic or predisposing factors, such as age, race, place and type of delivery, and important causes of death, are reviewed. In addition, statistical data have been presented on some of the principal causes of death in New York County, hemorrhage, infection and deaths associated with cesarean section and anesthesia. While it is admitted there are other important causes of death, an attempt has been made to emphasize the leading factors at the expense of omission of other phase of the problem. The following suggestions appear worthy of consideration.

1. The puerperal risk involved in the care of underprivileged, elderly, or colored patients is several times greater than that of young, white and the better situated economic group of patients. Lethal complications in the former may be sublethal in the latter. For these reasons such patients demand mature judgment and the best possible care at all times.

2. The more general adoption of local or regional block and greater restriction in the employment of general anesthesia.

3. The use of the classical cesarean operation should be limited to patients who are not in labor. The low flap operation is relatively safe during the early hours of labor; however, the dangers increase progressively as labor advances and the use of this procedure after fifteen or more hours of labor is accompanied by an unwarranted risk to the patient.

4. The employment of blood plasma where whole blood is not immediately available and the exclusion of crystalloid solutions is indicated for the immediate restoration of blood volume following hemorrhage to prevent the development of secondary shock.

5. Early recognition of the nature of infections and the prompt use of the appropriate sulfonamide drugs in adequate dosage where indicated.

6. Active participation by general practitioners and specialists in maternal welfare meetings, believing this medium to be the best available and a very satisfactory method of postgraduate instruction.

7. Assumption of the attitude that every obstetric death involves mistakes in judgment or technique and a constructive attempt to profit from the experience.

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Shock and Hemorrhage.—In 1939, not including deaths attributed to cesarean section, approximately one-sixth of the maternal mortality in New York City was attributed to this cause. In an analysis of the first 171 deaths studied by our Committee, as reported by Schneider,² approximately one-third of the deaths were ascribed to hemorrhage, when those from abortion and nonpuerperal causes were excluded.

I do not propose to present a statistical résumé of these cases, but rather a few impressions I have gathered from a study of the case records.

Briefly, the problem presented is the prompt control of hemorrhage and the immediate restoration of blood volume. For this latter purpose whole blood is undoubtedly superior to any of the other commonly employed solutions for infusion. However, it has been our experience that delay in transfusion occurs much too frequently with disastrous results. This can be corrected to some extent by having an available donor actually present or the employment of the blood bank when the possibility of hemorrhage may be anticipated. While preparations for transfusion are being made, blood substitutes are frequently necessary. Crystalloid solutions (saline and glucose) have the objection that the effect usually is only temporary, and second, they are useless in secondary shock which is associated with tissue anoxemia, increased capillary permeability, and acidosis. In actual practice their use may be more deleterious than beneficial. Colloid solutions (acacia), although they are better for purposes of restoring blood volume, must be administered slowly and with great care. Fatalities have been ascribed to their employment. Blood plasma on the other hand, has a number of advantages over these solutions for purposes of restoring blood volume.³⁻⁵ Briefly, pooled plasma with negative serologic reactions for syphilis may be stored under refrigerated conditions, for long periods of time and used as an infusion without delay when an emergency arises. Typing and determination of compatibility are not necessary. Reactions are relatively rare and innocuous and massive amounts may be employed, if necessary, without technical difficulties such as would be encountered in the procurement of an equal volume of whole blood from either a donor or blood bank source. Its prompt use following hemorrhage immediately restores blood volume and prevents the development of secondary shock. I am not advising the employment of plasma as a complete substitute for whole blood, but rather for the immediate restoration of blood volume by this means, instead of attempting to do so by the use of crystalloid solutions, as is common practice at the present time, while awaiting preparations for transfusion.

Infection.—We have been informed that slightly over 40 per cent of the puerperal mortality and slightly more than 23 per cent of the maternal mortality in New York City for 1939 was caused by infection. One year ago this month I presented evidence to this Society⁶ that the use of the sulfonamide group of drugs available at the time, in all postabortal and puerperal infections, was unjustified. The frequent employment of these preparations as indicated by the records studied at our Maternal Welfare Meetings appears to support the contention. In my opinion, early bacteriologic investigation into the nature of a given infection should constitute, as a general rule, the first step in the management of such patients. Frequently this has not been the case. Sulfonamide drugs may be indicated in serious fulminating infections before a bacteriologic report is available. This procedure should be the exception, however, rather than the rule.

I have been impressed by the data presented at our meetings concerning chemotherapy by several facts. Briefly, these include, inadequate dosage, lack of bacteriologic investigation, discontinuance of the drug because of "minor" toxic symptoms, changing from one drug to another for various reasons, and persistence in the use of the therapy in the absence of any signs of a favorable response.

Anesthesia.—In addition to the complications already cited when discussing cesarean section, there have been a number of other case records reported before our committee where general anesthesia was responsible to a large extent for the fatal outcome. Unfortunately, the total number of deaths caused by anesthesia in New York City are unknown because of lack of information, and it is interesting to note that only two deaths were attributed to this cause in 1939. Schneider,² however, reported 6 deaths due to asphyxia associated with anesthesia in his analysis of the first 171 deaths investigated by the New York County Committee. It would

TABLE II. HEMORRHAGE AND ACCIDENTS OF CHILDBIRTH

	1935	1936	1937	1938	1939
Puerperal deaths	197	156	158	127	110
Hemorrhage	20	25	21	19	13
Accidents of childbirth	44	36	34	33	29
Percentage of total	32.5	39	34.8	41	38.2

In this total of 76 deaths from septicemia, hemorrhage and accidents of childbirth account for 27 deaths of women who had cesarean section; 3 cesarean hysterectomies are included, 2 of which were for rupture of the uterus after failure of breech extraction, and 2 Waters' extraperitoneal sections, 1 after twenty-eight hours of labor with membranes ruptured seventeen hours, in which patient died of hemorrhage during the operation, and the other not in labor with death ascribed to shock. A general anesthetic was administered in 24 cases, local in only 3. The type of operation is of interest.

TABLE III. 110 PUERPERAL DEATHS, 1939; 27 CESAREAN SECTION DEATHS, 24.5 PER CENT

TYPE OF OPERATION	TOTAL	OPERATOR	
		OBSTETRICIAN	OTHER
Classical	15	7	8
Lower segment	7	7	—
Waters	2	2	—
Hysterectomy	3	3	—

To the classical operation is assigned the greatest number of deaths (15). It is noteworthy that intestinal obstruction caused death in 3 of these cases. In 8 women, not in labor, death was due to peritonitis (3) and intestinal obstruction (2), in the other 7 it will be seen that this operation was performed after many hours of labor, with death largely due to peritonitis.

TABLE IV. 15 CLASSICAL CESAREAN DEATHS, 1939*

HR. IN LABOR	HR. MEMBRANES RUPTURED	ANESTHESIA	DEATH
6	0	General	Peritonitis
6	6	General	Peritonitis
14	0	General	Eclampsia
28	0	Spinal	Obstruction
36	0	General	Peritonitis
36	24	General	Peritonitis
47	3	General	Peritonitis

*Eight not in labor. Peritonitis, 3, shock, 3, obstruction, 2; 7 in labor.

The lower segment operation was performed in 7 cases of cesarean section deaths, as shown in Table V.

TABLE V. 7 LOWER SEGMENT CESAREAN DEATHS

	HOURS IN LABOR	HOURS MEMBRANES RUPTURED	ANESTHESIA
Peritonitis	6	17	General
Peritonitis	10	16	Local, General
Peritonitis	15	39	General
Peritonitis	40	0	Local
Embolism	0	2	Local-Gas
Sepsis and embolism	5	6	General
Aspiration	13	8	General

PUERPERAL MORTALITY IN THE BOROUGH OF BROOKLYN, CITY OF NEW YORK*

CHARLES A. GORDON, M.D., F.A.C.S., BROOKLYN, N. Y.

THE number of puerperal deaths in the United States has declined sharply since 1933, the first year that figures from the entire country became available for study. In 1938 the national puerperal death rate was the lowest on record, a decline of 30 per cent from 62 per 10,000 live births to 43.5. The rate for 1939 will be still lower.

In New York City the rate has been more than cut in half since 1933, from 61.1 to 29.6 in 1939. In Brooklyn, however, the crude puerperal rate for 1939 was 26, the lowest in the five boroughs, with 110 deaths, while in 1933 there were 284 deaths, a rate of 70, which was considerably higher than the national and city rate that year. It has been shown, however, by Mr. Thomas J. Duffield, Registrar of Records of the Department of Health, City of New York, that the colored population of New York City, which is largest in Manhattan and Brooklyn, is an important statistical factor, since the puerperal death rate of colored women is nearly three times that of white women. And, since the death rate from abortion is nearly seven times as high among colored as white, Brooklyn is passed by Richmond and Manhattan when deaths early in pregnancy are excluded in calculating the maternal mortality rate.

In Brooklyn substantial reductions in all types of puerperal death have been made, but not uniformly. Deaths from hemorrhage, septicemia, and accidents of childbirth, which includes cesarean section, show a relative increase in the last five years.

In 1939 septicemia was charged with the greatest number of puerperal deaths, 31 per cent of the total, or 42 per cent if deaths from septic abortion exclusive of homicide are included. Only those deaths which are so reported by the Office of the Chief Medical Examiner are classified as criminal abortion. There are of course many more in which evidence is lacking. "It was because of 21 such cases, largely among colored women who died in Harlem, that the puerperal death rate in Manhattan was higher than that of Brooklyn."² Table I shows the relative increase of septicemia over a five-year period in Brooklyn, and the part played by operative delivery in 1939.

TABLE I. SEPTICEMIA, 1935 TO 1939

(Abortion excluded)

	1935	1936	1937	1938	1939
Puerperal deaths	197	156	158	127	110
Septicemia	49	45	39	37	34
Percentage of total	24.8	28.8	24.7	29	31
1939	Operations:		Associated:		
34 deaths	12 cesarean (peritonitis)		14 long labors		
	3 forceps		18 early rupture of membranes		
	4 version				
	5 induction		7 hemorrhages		

If deaths from hemorrhage are combined with those due to accidents of childbirth as largely due to hemorrhage and shock associated with delivery, we find a similar relative increase. Details are shown in Table II.

*Read at a meeting of the New York Obstetrical Society, Oct. 8, 1940.

enough. The educational value of committee discussion should not be overlooked. Individual interest on a large scale must be aroused, and every practitioner of obstetrics made to feel that he himself can make a worth-while contribution. This is essential. Education is continued by participation in the investigation and discussion of the all-important details appearing in the actual case records of puerperal death. The obstetric conference of the Committee on Analysis, wide open to every physician interested enough to attend, is an available and nearly perfect mechanism for that postgraduate education which we have found so difficult to provide for him. And, in the final analysis, solution of the medical problem lies in continued education.

256 JEFFERSON AVENUE

DISCUSSION

DR. BENJAMIN P. WATSON.—Each speaker has stressed that these committees in their discussions are not primarily concerned with individual responsibility or possible culpability, but only with the lessons that can be learned from any sins of omission or commission that may have occurred in the management of particular cases. They have wisely discarded the terms "preventability" and "nonpreventability" used in the original Academy of Medicine report, for around these two terms a great deal of the controversy, aroused by that report, raged. The terms were provocative. Looking back I, as one of the workers on that report, do not regret their use, for I believe that they, more than anything else, were responsible for the awakening of the medical profession to the necessity of looking further into this matter and for the establishment of the constructive work now being done by the Maternal Welfare Committees not only in Greater New York, but throughout the country. As both speakers have said, these meetings, open as they are to every member of the profession, are of real educational value and cannot but play a large part in the promotion of better obstetrics.

The reduction in maternal mortality in New York and throughout the country in the last three years has been most remarkable. I believe that the repeated statement of the problem in medical and lay meetings and journals has played a significant part in stimulating individual practitioners to do better work and to get better results. Any doctor who attends these Committee Meetings regularly and hears at meeting after meeting the same type of case discussed, the same mistake made in each case, the same want of foresight, and as a result, the same haste and confusion when emergency arises, must be better able to deal with that type of case when he himself encounters it.

Prenatal care resulting in the early detection and treatment of pregnancy toxemia, in the adequate treatment of cardiac and other complications, accounts for a large percentage of the total reduction in maternal mortality.

It is evident, however, from the facts given us by both speakers that a determined drive has to be made to inform the profession of the danger of operative obstetrics and of the necessity for making every provision for every possible emergency that may arise in its course. Dr. Gordon has told us how, as a result of their discussions in Brooklyn, standards of operative practice have been formulated, the necessity for close scrutiny of the indications for cesarean section, the importance of the type of anesthesia, the provision of blood by the presence of a donor or the accessibility of a blood bank, the proper preparations to make before the handling of a case of placenta previa, adherent placenta, or inversion of the uterus.

The fatalities in the course of and following operative obstetrics are usually the result of haste and confusion, because these provisions have not been made beforehand.

Since cesarean appears as a cause of death in 27 of the 110 cases of puerperal death in 1939, a ratio of 1 to 4, it has seemed wise to present it thus in detail. The Bureau of Vital Statistics has assigned 12 of these deaths to septicemia. It is clear then that reduction in the number of cesarean deaths will lower considerably the number of deaths in this rubric.

Anesthesia in itself is a definite hazard. During the three-year period, 1937 to 1939, anesthesia was the actual cause of death in 13 cases in the entire number of 395 puerperal deaths. If this may be compared with 20 in the 2,041 deaths analyzed in the New York Academy of Medicine report, more than three times as many deaths occurred from anesthesia as might be expected. In 9 of these cases there were definite controllable factors, as the use of ether in toxemia (2), spinal anesthesia for cesarean during cardiac decompensation (1), inexperienced anesthetist (1), and vomiting with aspiration (5).

All too often certificates of death are written by interns or others not interested in accurate reports of puerperal deaths or unfamiliar with statistical implications. Yet at best the true importance of anesthesia is unknown under the present method of coding.

We have found that our placenta previa mortality was largely due to procrastination. In no case did initial hemorrhage cause death. In 18 out of 24 cases, repeated hemorrhage occurred before any treatment was instituted, a week or more elapsing in 12 cases. Transfusions were often inadequate.

Inspired by a visit to Philadelphia where analysis of puerperal deaths was going on, a similar study was begun in Brooklyn in 1936. With the excellent cooperation of the Commissioner of Health, the Maternity Center Division of the Visiting Nurse Association of Brooklyn and formal representation from every hospital, we have been able to get a perfect return of case histories. For three years we have assigned preventability of death, yet we long ago discovered that it is easy to do this only when a small committee of obstetricians sits in judgment. Time and again, at large meetings, we have been unable to form an opinion or have reversed our own previous decisions. Actually it is impossible to define preventability with scientific exactness, and it should be done that way or not at all. The very word implies a criticism not intended. Preventability statistics have served their purpose. Now we discuss controllable factors, planning and building up discussion and striving to establish standards of practice so far as that may be done, and using the word "preventable" only for stimulation of discussion.

It should be said that these meetings are well attended by obstetricians and general practitioners, interns and residents. No hospital or physician is identified in the discussion. Every physician in Brooklyn is invited and urged to attend, and everyone present has a voice, and a vote if one should be taken. The Committee on Analysis has become a committee of the entire profession, with its only purpose self-education. Once a year results are summarized and presented at an open meeting of the Brooklyn Gynecological Society.

It is idle, of course, to believe that any educational method will reach every physician, yet lessons learned by those present must eventually become widely diffused. And the knowledge that every puerperal death is under scrutiny operates for the benefit of the patient. It has been made clear that responsibility for the patient's welfare does not rest entirely with the physician. Not only do women have a right to expect every hospital to be a safe place for delivery, but the best interests of patient, hospital, and physician are served in no other way. More and more hospitals require consultation in all cases of long labor, hemorrhage, toxemia, and all operative procedures other than low forceps, and advice and help are available without fee, when the patient's physician feels that the situation should be managed that way.

That standards of practice become fairly well established after repeated group discussion is inevitable. The purpose of this paper is to call attention to the value of this teaching method as a source of inspiration for obstetrician and general practitioner alike.

Enough has been said to show that operative delivery, particularly cesarean section, is the heart of the Brooklyn problem. Any committee on analysis, able to inquire into all the circumstances of death, can just as readily outline its own situation. Certainly no problem can be solved until it is clearly stated. Yet this is not

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF NOVEMBER 7, 1940

The following papers were presented:

Report on Clinics—Woman's Medical College Hospital. Dr. Lewis C. Scheffey.
The Effect of Combined Administration of Chorionic Gonadotropin and the Pituitary Synergist on the Human Ovaries. Drs. Charles Mazer and Elkin Ravetz. (For original article, see page 474.)

Pubertas Praecox Due to Ovarian Tumor. Dr. Clifford B. Lull. (For original article, see page 445.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 18, 1940

The following papers were presented:

Amenorrhea and Sterility Caused by Bilateral Polycystic Ovaries. Dr. M. L. Leventhal. (For original article, see page 516.)

Report of a Case of Intravasation. Dr. E. W. Fischmann.

The Late Effects of the Toxemias of Pregnancy. Dr. John H. Moore, Grand Forks, N. D. (by invitation).

Some Observations on the Gynecic Employment of Equine Gonadotropins. E. C. Hamblen (by invitation). (For original article, see page 495.)

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF NOVEMBER 19, 1940

The following paper was presented:

The Treatment of Pelvic Endometriosis. Dr. Walter T. Dannreuther (by invitation). (For original article, see page 461.)

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 7, 1940

The following papers were presented:

Deep Cauterization of the Cervix. Drs. B. Z. Cashman and J. S. Frank. (For original article, see page 379.)

The Clinical Evaluation of Stilbestrol. Dr. Jos. A. Hepp.

Society Transactions

AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS AND ABDOMINAL SURGEONS

*FIFTY-THIRD ANNUAL MEETING, EXCELSIOR SPRINGS, MO.
SEPTEMBER 26 TO 28, 1940*

The following papers were presented:

- Home Delivery Service for Medical Students.** Dr. Calvin R. Hannah, Dallas, Texas. (For original article, see page 417.)
- Deep Cauterization of the Cervix.** Drs. B. Z. Cashman and John S. Frank, Pittsburgh, Pa. (For original article, see page 379.)
- A Skin Test for the Diagnosis of Pregnancy.** Drs. Frederick H. Falls, V. C. Freda, and H. H. Cohen, Chicago, Ill. (For original article, see page 431.)
- Transmigration of the Human Ovum.** Dr. Q. U. Newell, St. Louis, Mo.
- The Effects of Analgesia on the Newborn Infant.** Dr. C. O. McCormick, Indianapolis, Ind. (For original article, see page 391.)
- The Palatal Arch and the Pelvis.** Drs. A. J. Rongy and A. B. Tamis, New York, N. Y.
- Acidosis and Alkalosis in Obstetrics and Gynecology.** Dr. W. T. Pride, J. R. Reinberger, and D. T. Holland, Memphis, Tenn. (For original article, see page 412.)
- Pubertas Praecox Due to Ovarian Tumors.** Dr. Clifford B. Lull, Philadelphia, Pa. (by invitation). (For original article, see page 445.)
- Objections to Induction of Labor in Normal Pregnant Women.** Dr. E. L. Cornell, Chicago, Ill. (For original article, see page 438.)
- A Report of a Series of Complete Tears of the Perineum With Extension up the Posterior Vaginal Wall, Repaired by the Vaginal Flap Method.** Dr. Ralph E. Campbell, Madison, Wis. (For original article, see page 403.)
- The Theca Cone and Its Tropism Toward the Ovarian Surface, A Typical Feature of Growing Human and Mammalian Follicles.** Dr. Erwin O. Strassmann, Houston, Texas. (For original article, see page 363.)
- The Psychology of Pregnancy.** Dr. Stuart B. Blakely, Binghamton, N. Y.
- Re-operation: Analysis of 125 Gynecological Cases.** Dr. E. Lee Dorsett, St. Louis, Mo.
- Clinical Experience With Testicular Extract in Obstetrics and Gynecology.** Dr. David Hadden, Oakland, Calif.
- Actinomycosis of the Ovary.** Dr. W. A. Coventry, Duluth, Minn. (For original article, see page 455.)
- Nationality and Carcinoma of the Cervix.** Dr. Frank R. Smith, New York, N. Y. (For original article, see page 424.)
- Some Remarks About Maternal Mortality in the South.** Presidential Address. Dr. James R. McCord, Atlanta, Ga. (For original article, see page 355.)

NEW YORK OBSTETRICAL SOCIETY

MEETING OF OCTOBER 8, 1940

The following papers were presented:

- Menstruation and Urination Through a Clitorislike Structure.** Drs. David N. Barrows and Winston N. Bloch. (For original article, see page 513.)
- Puerperal Mortality in the Borough of Brooklyn, City of New York.** Dr. Charles A. Gordon. (For original article, see page 535.)
- A Study of Puerperal Mortality in New York City (1937-1940) with Special Reference to Preventive Factors.** Dr. R. G. Douglas. (For original article, see page 529.)

Olovson, T.: *Bilateral Extrauterine Pregnancy*, *Acta obst. et gynec. Scandinav.* 18: 380, 1938.

Olovson reports a case of bilateral extrauterine gestation and collected 158 additional cases from the literature. He points out the necessity for exploring both tubes in all cases when operating for a tubal pregnancy.

J. P. GREENHILL.

Gaines, Collins, and Brown: *Abdominal Pregnancy*, *South. M. J.* 31: 1278, 1938.

The histories of two patients with this relatively rare condition are presented in detail. The first was a 25-year-old primigravid negress who was admitted to the hospital in the seventh month of pregnancy. Beginning at about the second month, and persisting from time to time throughout the gestation, she experienced epigastric and right upper quadrant pain, gaseous eructation, and occasional vomiting. During this period there was a weight loss of 40 pounds. Fetal movements were first felt two months before admission and caused mild pains, and vomiting after meals. Three days previous to her arrival at the hospital they were accompanied by severe shooting pains in the upper abdomen, with dull aching pains and a sensation of heaviness in the pelvis. Abdominal enlargement corresponded to that of a full term gestation, and the baby lay in the upper half of the abdomen. To the left of the midline in the lower abdomen, and rising to the height of a four to five months' pregnancy, a spongy mass was felt. This was interpreted as uterine fundus. The cervix was firm, and there was no indication of dilatation or effacement, and the pelvis was empty. A clinical diagnosis of extrauterine pregnancy was confirmed by x-ray studies which demonstrated the fetus lying transversely across the upper abdomen just beneath the diaphragm. Under local anesthesia a left rectus incision was made. The placenta was found in the midline extending to the left and attached to the lower abdominal viscera and the uterus. The baby lay free in the peritoneal cavity, weighed 4 pounds and 2 ounces, and died seven hours later. During the postoperative course, there was hemorrhage upon 3 occasions, and the patient died on the thirteenth day.

The second patient was a 26-year-old colored multipara whose prenatal course was uneventful except for the fact that fetal movements had not been felt for one month before admission. The abdomen was the size of a full-term gestation, fetal heart tones were not audible. The pelvis was empty, and there was no cervical dilatation or effacement. Medical induction was not successful. She was discharged to prenatal clinic, and, because of toxemia, was readmitted for medical induction which again failed. Fetal movements and heart tones were absent. A fetal head was palpated at the umbilicus with crepitation. The Friedman test was negative. Surgical induction of labor was unsuccessful. Following an x-ray examination, a diagnosis of probable extrauterine gestation with dead fetus was made. At laparotomy, a full-term macerated fetus was found lying free in the peritoneal cavity. The abdomen was closed with drainage. Convalescence was essentially uneventful, and the patient was discharged on the fifteenth day.

ARNOLD GOLDBERGER.

Russell, B. P., Jr., and Black, W. T., Jr.: *Primary Ovarian Pregnancy*, *South. Surgeon* 9: 114, 1940.

Primary ovarian pregnancy is a rare condition in which the fertilized ovum undergoes a certain stage of its development entirely within the ovary. In secondary ovarian pregnancy, the ovum, following its fertilization, undergoes some of its development in a nearby structure, usually the Fallopian tube, and then becomes implanted on the ovary. The literature contains 85 supposedly proved cases of primary ovarian pregnancy. The authors, in a review of the reports, found 52 cases in which the criteria for the primary condition existed as defined by Sutton. They report a new proved case of primary ovarian pregnancy.

The patient, 23 years of age, was pregnant for the second time. Following an amenorrhea of approximately eight weeks, there was nausea, severe lower abdominal pain, and vaginal bleeding. On admission temperature was 98.6° F., pulse 60,

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

✓ Ectopic Pregnancy

Rojdestvenskaia, A. J.: *The Etiology of Extra-Uterine Pregnancy*, Surg., Gynec., Obst. 67: 308, 1938.

The etiology of tubal pregnancy may depend on three factors: (1) the ovum developing its capacity for implantation before it reaches the uterus; (2) disturbed transportation of the ovum; (3) mechanical obstacles encountered by the ovum on its journey.

All three factors are closely connected with one another and therefore their distinction of one from another can be only approximate. However, the outstanding cause, apparently is the second factor, i.e., disturbed transportation of the ovum, for in all probability it may be the independent cause of tubal pregnancy, while the first and third factors, in particular (i.e., mechanical obstacles), play merely a relative part and must be accompanied by disturbed transportation, however slight, to cause tubal pregnancy.

The motor capacity of the tube depends to a great extent on the effect of the vegetative nervous system, which in its turn may be influenced by various emotions: fear of pregnancy, abortion, and the use of contraceptive measures.

From a study of 100 cases of tubal pregnancy, it is believed that the cause of the faulty implantation was the first factor in 10 per cent of cases, and the third in 76 per cent.

Among the mechanical causes, defective development of the tube of postembryonic nature seems to be of greatest importance.

Improvements in living conditions, less frequent occurrence of infectious diseases, and better working conditions for growing girls will reduce the percentage of extrauterine pregnancies.

WILLIAM C. HENSKE.

Villaca, Joao: *Ectopic Pregnancy*, Rev. de gynec. e. d'obst. 2: 172, 1938.

The author presents a study of 20 cases of ectopic pregnancy. Three patients with abortion through the tube were operated upon and discharged cured; 7 instances of ruptured tubal pregnancy, all operated upon, with 1 death due to paralytic ileus; 1 patient with interstitial tubal pregnancy of eight months, 2 cases of lithopedion, 2 cases of abdominal pregnancy, 2 with supposed tumors of the ovary, which proved to be tubal pregnancies all operated upon; 1 of them with cirrhosis of the liver died postoperatively.

Thus of the 20 cases of extrauterine pregnancy reported, all patients were operated upon with two deaths.

MARIO A. CASTALLO.

Caccia, J. P.: *Repeated Tubal Pregnancy*, Semana méd 47: 583, 1940.

From a review of the literature and a study of his own cases, Caccia concludes that recurrence of tubal pregnancy in the same woman takes place in about 4.14 per cent of cases. Such recurrences may be observed from two months to fifteen years after the first ectopic pregnancy. However, during this interval, normal intrauterine pregnancies may occur. The frequency of such normal gestations was 32 per cent. Hence, there is no justification for avoiding plastic operations on pregnant tubes because of the fear of a repetition of an ectopic pregnancy.

J. P. GREENHILL.

difference in age of these two pregnancies, determined from the stage of ripeness of the follicle, cannot be considerable and hardly over three weeks.

The reported case is also a classical example of external migration as shown in the right tubal pregnancy which originated from the left ovary. After the relatively long travel from left ovary to right tube, the left tube being closed at its fimbriated end, the impregnated ovum was ready for nidation and implanted itself in the middle of the tube.

J. P. GREENHILL.

Stern, S. I.: Intramural Pregnancy, *Gynéc. et obst.* 38: 193, 1938.

Intramural pregnancy is defined as a variety of ectopic gestation in which the ovum becomes implanted in the wall of the uterus, developing between the muscle layers. The author agrees with those writers who distinguish between intramural and interstitial pregnancy.

In a ten-year period, this condition was encountered twice in a series of 380 laparotomies performed for ectopic gestation, an incidence of 0.51 per cent. Of these one was a pure form of the condition, the other a mixed one. Both patients became pregnant again shortly after operative intervention, and were delivered of normal infants at term. The factors commonly discussed in connection with the etiology of ectopic gestation are reviewed.

The first patient, a 40-year-old multipara, had 13 full-term gestations and one miscarriage at three months, with a lapse of ten years since the previous gestation. Her last period occurred three weeks previously, and was late. She was admitted to the gynecologic service in a critical condition with signs of intra-abdominal hemorrhage. At operation the peritoneal cavity was full of blood, and at the region of the right uterine horn, there was a small nodular elevation near to a perforation. A small cavity, 4 mm. in diameter, the site of the implanted ovum, was filled with blood clot. The cornu was excised down to the mucosa, together with a portion of the tube, and peritonization was effected. On the fourteenth day postoperative, the patient was discharged in good condition. *Histologic diagnosis:* Intramural gestation, the site of implantation formed by the muscle layers of the uterus; villi take the stain well.

The second patient, aged 37 years, had one previous stillbirth. She was admitted to the hospital in shock, with signs of an intra-abdominal emergency. Following a two-month period of amenorrhea, and one week before admission, there was a bloody vaginal discharge followed by severe abdominal pain and syncope. At operation considerable blood was found in the peritoneal cavity, and in the isthmus portion of the left tube at the site of its origin from the uterus, there was an ectopic gestation. There was uneventful recovery of the patient. Histologic examination of the specimen revealed tubouterine pregnancy.

The author regretted his inability to make a detailed histologic study of the specimens, with the possibility of thus throwing more light upon the etiology of this condition. Ordinarily, the perforation occurs on the posterior surface of the fundus of the uterus; it is due to destruction of the muscle wall by placental villi.

ARNOLD GOLDBERGER.

Limpach, L., and Boy, J.: Tuberculosis of the Fallopian Tubes and Ectopic Pregnancy, *Gynéc. et obst.* 38: 359, 1938.

Statistical reports indicate that 60 to 80 per cent of women with genital tuberculosis are sterile. Anatomic lesions, in addition to functional disturbances, are the factors chiefly responsible for this sterility. Should pregnancy occur, complications may ensue; of these, ectopic gestation is rare.

A 32-year-old nullipara who had been married for four years was admitted to the hospital with a history of amenorrhea of two months' duration, a bloody vaginal discharge upon one occasion, and violent lower abdominal pains. Ectopic pregnancy in left tube was suspected and the patient placed under observation. The Aschheim-Zondek test was positive. Nine days after admission acute lower abdominal pain recurred following the taking of castor oil. At laparotomy the peritoneal cavity was filled with blood, and there was a left hematosalpinx which

and respiration 22. The patient perspired profusely and her skin was cold and clammy. There was some vaginal bleeding, and the chief complaints were nausea and severe lower abdominal pain. Laboratory studies showed: 3,570,000 red blood cells; 9.3 Gm. hemoglobin; 26,700 white cells, with 71 per cent polymorphonuclears. Because of an almost classic history of ectopic pregnancy, laparotomy was decided upon. Preliminary vaginal examination revealed a small uterus which was freely movable. There were no adnexal masses, but the right ovary was palpable. A soft mass was palpated in the cul-de-sac.

There was free blood in the peritoneal cavity, both tubes were normal and the right ovary was slightly cystic; a soft mass of bloody tissue in the cul-de-sac contained a placenta and fetus. In the left ovary there was a bleeding crater approximately 2 cm. in diameter, with adherent placental tissue. Left salpingo-oophorectomy was performed. The crown to heel length of the fetus was 78 mm., and its estimated age was 13 to 14 weeks. The Fallopian tube was 5 cm. in length and its lumen patent with masses of clotted blood at the fimbriated end. Microscopically, there was evidence of edema and hyperemia, but the mucosa was intact and no placental tissue was observed either in the tube or in the blood clot adherent to the fimbriae. Grossly, the lacerated portion of the ovary measured 2.2 cm. in diameter, and 1.2 mm. in depth. Histologic study of this area revealed edematous ovarian tissue, hemorrhage with fibrin clot, a convoluted layer of lutein cells, and chorionic villi within the ovarian tissue of adjacent areas.

It is suggested that all primary ovarian pregnancies develop upon the basis of pathologic changes in the ovary whereby ovulation is prevented by thickening of the theca or an unusually firm attachment of the ovum to the discus proligerus. In either case, there is retention of the ovum in the follicle. In this instance the ovarian stroma contained numerous follicle cysts. In the history of these patients, it is a noteworthy fact that periodic sterility is common.

To the accepted criteria for the establishment of the diagnosis of primary ovarian pregnancy, the authors wish to add the requirement that serial histologic sections of the tube on the affected side prove that rupture has not occurred.

ARNOLD GOLDBERGER.

Bittmann, O.: A Case of Simultaneous Tubal and Ovarian Pregnancy, Monatschr. f. Geburtsh. u. Gynäk. 110: 17, 1939.

Bittmann reports the very rare if not unique observation of simultaneous extra-uterine tubal and ovarian pregnancy in a 33-year-old woman. Both ova, implanted in the right tube and right ovary, were entirely separated from one another, so that the possibility of a tuboovarian pregnancy need not be discussed. The ovarian pregnancy was imbedded in a Graafian follicle; the right tubal pregnancy had its own corpus luteum in the left ovary. Histologic serial section of the resected right ovary gave no evidence of follicles with two or more ova.

Judging by this case as well as by another one of follicular pregnancy, one comes to the conclusion that a purely follicular pregnancy can only originate where the follicle has just burst and the opening caused by rupture is not yet closed, i.e., before fibrinoid transformation of the opening occurs. To be fertilized at all, the ovum must lie near the place of rupture which however must be very small. Moreover, the ovum must adhere in this place more firmly than usually, it must still be in firm communication with the granulosa cell stratum of the cumulus ovigerus; last, the inside pressure in the follicle must be lower than normal. An ovum fertilized in this place is very likely to have special energy toward implantation and nidation, for, although an ovum impregnated in this place also finds a nutritive epithelial medium, this is rather poor compared to the uterine and even to tubal mucosa. Histologically, the progress of such pregnancies is similar to conditions in placenta previa, especially in placenta previa cervicalis.

Based on the removed specimens it can be said that in this case the two fertilized ova must have been of different age, i.e., the result of different fecundations. The follicular pregnancy in the right ovary originated first. This leads one to consider whether one had to deal with a case of superfetation or of superfecundation. The author thinks that superfetation occurred in this case. The

Items

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Cleveland, Ohio, by the entire Board from Wednesday, May 28, to Monday, June 2, 1941, inclusive, prior to the opening of the annual meeting of the American Medical Association in Cleveland.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reevaluation* in Part II must make written application to the Secretary's Office before April 15, 1941.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

This Board will hold its annual dinner for Diplomates, and others interested in the work of the Board, on Wednesday evening, June 4, 1941, at the Wade Park Manor Hotel, Cleveland, Ohio, immediately following the close of the Part II examinations, which will be conducted in Cleveland in the spring, immediately prior to the opening of the annual A. M. A. meeting.

The Journal of Clinical Endocrinology

A new monthly magazine devoted to this field, which is maintained by and issued for the Association for the Study of Internal Secretions, is being published by Charles C. Thomas of Springfield, Ill. It will cover the practical aspects of endocrine medicine, including diagnosis and therapy, symposia and reviews, original research. The Managing Editor is Dr. Milton Lee, of Boston, and there is a Publication Committee of well-known specialists and research workers. The new journal is designed to supplement the well-known and established *Endocrinology* which will continue to present articles on experimental research.

had ruptured in the region of the ampulla. The left adnexa were removed. Post-operative convalescence was uneventful.

Histopathologic examination revealed numerous double layered placental villi, and the characteristic features of an hyperplastic tuberculous salpingitis.

This case is unusual because pelvic tuberculosis rarely causes ectopic gestation; complete tubal occlusion with absolute sterility is the usual result.

ARNOLD GOLDBERGER.

Garcia, P., and Tisne, L.: *Endometriosis and Tubal Pregnancy*, Bol. Soc. chilena de obst. y ginec. 4: 493, 1939.

The authors present a case of tubal pregnancy associated with endometriosis. They feel that the latter condition is more often a cause of ectopic pregnancy than is commonly realized and recommend the careful histologic study of tubes involved in this condition. The article contains several excellent microphotographs.

R. J. WEISSMAN.

Dubourc, G., and Mahon, R.: *Importance of Histologic Examination of the Decidua in the Diagnosis of Extra-Uterine Pregnancy*, Rev. franç. de gynéc. et d'obst. 34: 42, 1939.

The authors call attention to the decidua in cases of extrauterine pregnancy and also to the fact that frequently pieces of decidua are considered to be an aborted ovum. Microscopic examination alone suffices to distinguish between decidua and ovum and hence, the differentiation between an intrauterine abortion and a pseudo-abortion of an ectopic pregnancy. Therefore, in all doubtful cases a histologic examination should be made of all the tissue which is expelled from the uterus or obtained by an exploratory curettement.

J. P. GREENHILL.

Dubrausky and Martzy: *Significance of the Friedman Pregnancy Test in the Diagnosis of Extra-Uterine Pregnancy*, Klin. Wchnschr. 18: 600, 1939.

The authors report the results of their findings in 69 cases of extrauterine pregnancy. Of these, 24 were acute and 45 chronic. They concluded from their studies that the Friedman pregnancy test has no great diagnostic value in the acute type of extrauterine pregnancy (i.e., with rupture). They arrive at this conclusion first, because the urgency of the case does not permit the time necessary for the carrying out of the test, and second, because of the inaccuracy of this test in the patient with the acute type of pathology. In the so-called chronic type, the Friedman test has some diagnostic value, but they caution against relying upon the test as a means of diagnosis. It should simply be used as a means of confirming other clinical and laboratory tests.

RALPH A. REIS.

Köberle, F.: *Tubo-Uterine Abortion*, Zentralbl. f. Gynäk. 63: 1181, 1939.

Köberle reports the case of a 35-year-old woman who expelled a 35 mm. embryo from the vagina, one and one-half months after her last menses. Twelve days after the abortion the woman died. Autopsy revealed marked anemia due to intra-abdominal bleeding from a ruptured right Fallopian tube which was the seat of an ectopic pregnancy. Because of the location of the ovum in the isthmus of the tube, just at the junction with the uterus, the author assumes that during the course of the pregnancy the interstitial part of the uterus dilated and through this the fetus escaped into the vagina. The small rupture in the tube took place at the time when the fetus was expelled.

J. P. GREENHILL.

The first phase of improved medical education was the elimination of the weak, poorly equipped medical schools with which the country was afflicted forty years ago. Rapid population growth, due to unrestricted immigration and the high birth rate, created a demand for physicians, which led to a mushroom growth of nearly 400 incompetent schools—veritable “doctor factories” and “diploma mills” turning loose hundreds of incompetent so-called doctors pitifully ignorant and unskilled.

This first phase of improvement was accomplished by classification of schools by the American Medical Association, which gradually eliminated the weaker schools and raised the quality of teaching in the others.

The second phase of improvement was the elevation of educational requirements for admission to medical schools. This was brought about by educators themselves, who appreciated the fact that their students were unprepared to receive instruction in scientific medicine. An inevitable and concomitant feature of low-grade medical schools was inadequate admission requirements. To correct this deficiency high school graduation was the first added requirement for entrance into medical schools; then successively one, two, and three years of college work with certain subject requirements, and in several schools a bachelor's degree was demanded.

The third phase of improvement was the broadening of the medical undergraduate course, first, by increasing its length to four years; second, by increasing its scientific content by the addition of well-equipped and well-manned laboratories; and third, by augmenting clinical teaching with controlled hospitals under the supervision of well-trained full and part-time teachers.

The fourth phase was the improvement of the required and voluntary internships by raising their educational value through increased length of service and by better teaching. This was aided by the classification of hospitals according to the educational desirability of their internships, especially by schools which required five years to obtain the doctor's degree.

The fifth phase of improvement was the conversion of residencies from a mere long-time internship to an organized, extended training on a real graduate basis under well-trained and experienced teachers, the same as in other departments of learning.

Many medical schools have become departments of universities; hence they must conform to the standards of the graduate school and be responsible to the Dean of that school and to the President. This insures a well-educated and technically well-trained graduate student capable of, at least, beginning the practice of his specialty.

Now that better training is available and the competency of the specialist may be certified by the specialty boards, it is no longer necessary for the public to put up with the “specialist” by evolution from general practice or the six-weeks so-called training in an inferior post-graduate school, or the specialist by announcement. However, there are not enough educationally high-class residencies to supply the de-

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PRESIDENTIAL ADDRESS

CONTINUATION STUDY

POSTGRADUATE EDUCATION—AN EXPERIMENT

JENNINGS C. LITZENBERG, M.D., MINNEAPOLIS, MINN.

IT SO happens that the span of my professional life coincides with the evolution, one might even say revolution, of American medical education. I have watched its developments through four decades, and have seen with wonder and admiration how it has kept pace with the compelling forces of science in every field of endeavor. When I entered the university fifty years ago, inventive genius had not yet dreamed of the automobile, moving pictures, or the airplane; the x-ray, wireless telegraphy, and the radio were yet unborn, and the phonograph was only a curiosity. Most of the inventions which are commonplace today were unknown.

The forty years of this century have witnessed greater progress in the world of science than the forty preceding centuries. As we contemplate, in retrospect, the astonishing progress in science and medicine, we marvel that the mind of man can digest it. With our amazement at the unfolding secrets of science and medicine, it is indeed gratifying to know that medical education has kept pace with it all.

The increasing dimensions of medical education are a measure of, and a tribute to, the judgment and courage of medical educators in the face of great difficulties, in correcting the weaknesses and in meeting the problems of rapidly expanding scientific knowledge. The improvements in medical education have been their answers to certain evils or needs and they can be differentiated into quite distinct phases.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

The real objective in the residency or fellowship is the training of a specialist over a sufficient length of time and of such a high educational quality that the finished product will redound to the credit of the hospital, insure better care of patients, and elevate the standards of medical practice.

The sixth phase in the development of medical education is postgraduate work. In the past, the term "postgraduate" bore a rather unsavory stigma because of the numerous low-grade "fly-by-night" schools which, in six weeks, produced "specialists" certified with a gloriously engraved diploma. Higher grade institutions objected to being classed with these shoddy postgraduate institutions, so they renounced the distasteful appellation and adopted the designation "graduate school." Some of the better postgraduate schools raised the quality of their teaching and became affiliated with universities.

In recent years postgraduate study has acquired a new meaning and dignity. It is now generally recognized that it is a needed development in medical education.

So important have the developments in graduate and postgraduate study become that the Advisory Board of Medical Specialties created in 1937 the Commission on Graduate Medical Education "to study the whole problem," including the internship, and graduate and postgraduate medical education.

The Commission's report, of 293 pages, emphasizes the great need for postgraduate education for the physician without too much interruption of his practice, refers to the many divergent plans for continuation study (a better term than postgraduate education), indicates their strength and weakness, and impressively insists that they must conform to highest educational standards, which, of course, is the crux of any teaching plan. In short, the report insists that, while all experiments contain something good, they all need critical analysis and some coordinating force which will secure "high standards but not standardization."

It seems rather trite to say that medicine and its allied sciences are changing so rapidly that the physician can keep abreast of progress only by continuous study after graduation. But self-improvement at home is not enough. Organized opportunities for further study, under proper educational supervision, are also necessary.

Such organized facilities first became available in a meager and halting way about two decades ago. Especially in the last ten years various and sundry courses have been offered in almost all the states. While many physicians have availed themselves of these opportunities, the response in general has been somewhat disappointing. One of the great problems of continuation study courses is to stimulate wider interest in them. The best advertising is the quality of the courses; their content to meet the needs of the physician in practice, and trained men to do the teaching.

Many experiments have been made which the Commission declares is "a desirable condition which must continue if healthy growth is to endure. Educational standards can be developed with a wide latitude

mand of those who wish to become well-trained specialists able to pass the examinations of the specialty boards.

Hospitals connected with educational institutions are doing their part, but additional adequate residencies can only be supplied by larger hospitals which have no connection with medical schools. Many of them now offer residencies which may fall far short of the educational standards required for good graduate training; they frequently are nothing more than long internships. Their need is for higher educational standards by proper organization of a staff of specialists, teaching on a university basis, and the help of medical school teachers to raise their standards.

Here is another condition which the members of this Association can alter by insisting upon good teaching in the hospitals where they work.

Hospital staffs must realize that the intern and resident are not in the hospital just to help in operations and otherwise care for patients, but to receive an education as well. Room, board, and uniforms are not sufficient remuneration for the valuable services they render. They earn "good money" and should get it in the form of constant careful teaching in all the details of diagnosis and treatment.

When the time comes that these compensations are given, the staff members will be rewarded by better care of their patients. The reputation of the hospital will grow and it will be able to secure the best type of interns and residents, and eventually it will be accredited as a high-grade teaching hospital. When enough hospitals realize this responsibility, the needed residencies will be forthcoming and the welfare of the people will be in better hands.

Of the five phases of improvement of medical education mentioned, the first phase, the elimination of weak schools, is all but finished. The second phase, increased entrance requirements, nears solution. The third phase, the improvement of the undergraduate medical course, has developed a philosophy of education which renders its ultimate solution certain. The fourth phase, the internship, is progressing toward a satisfactory solution in teaching hospitals, but in hospitals not affiliated with teaching institutions too little has been accomplished and nothing can be expected until their staffs fully appreciate their obligation. The fifth phase, the broadened training of residents and fellows, has reached a high plane in hospitals connected or affiliated with medical schools. The weakness is in hospitals not associated with teaching institutions, where clinical experience and development of skills are not accompanied by proper teaching and training in research founded upon broad and sound pedagogic principles.

The demands for residencies and fellowships cannot be supplied by teaching hospitals. The Commission on Graduate Medical Education estimates that 50 per cent more residencies are needed for ambitious young men who desire better training for a specialty and to meet the requirements of specialty boards, which in 1942, will be increased by all boards to three full years residency or the equivalent. I fear that this need cannot be met until hospitals without teaching facilities realize that they owe an educational obligation beyond clinical experience and development of technical skill.

May I quote the Commission's final paragraph on postgraduate education:

"The time is now ripe for the development of broad standards of educational content of postgraduate work, standards that will emphasize objectives and stimulate higher achievement without inhibiting widespread experimentation with means and methods.

"Perhaps the most difficult problem is to recruit and train teachers who will be able to hold the attention of practicing physicians. Teachers must learn to present their subject matter in a form that is condensed and so organized that it closely integrates the applicable basic science material with practical diagnostic and therapeutic techniques. To make postgraduate study effective and of good educational content, it should be considered a continuation of undergraduate and graduate medical education."

It is obvious that this last phase of improvement of medical education is not a "thing apart" but "part and parcel" of that great movement to keep medical education abreast of scientific progress, which began just before the turn of the century, gaining momentum with each decade, actuated by the philosophy of "broad standards of educational values." We must now apply the same principles to postgraduate education, continuation study.

The heterogeneous mass of differing plans and methods must be crystallized into a sound educational philosophy. The elements are already in the mass, and the water of crystallization will be supplied by medical educators, the profession, and all organizations interested in the solution. I have no disposition to worry you with an attempt to analyze the various types of courses given to further continuation study. They are good but they may be made better. You are all familiar with refresher courses, long or short, given at or near the physician's home; courses given at medical centers; intensive courses by general and special medical societies; circuit courses by traveling teachers and consultants; courses given annually by state societies, clinical congresses, regional postgraduate assemblies, and the courses on specific subjects like the ones sponsored by the Maternal and Child Welfare Committee.

They all have their good features and their drawbacks. It may be said in general that the short courses given at or near the physician's home have the advantage of reaching more doctors, but the disadvantage that the exigencies of an active practice prevent many from attending the daily sessions. On the other hand, courses given at a medical school center have the advantages of greater educational value by virtue of a larger number of trained teachers, more hospital clinical material for demonstrations, laboratory facilities, and proximity to a large library, with nothing at all to interfere with the courses.

The Commission has cited the University of Minnesota as an example of advantageous postgraduate teaching in a center. The University has taken the matter of adult education very seriously. On its campus is a large building, The Center for Continuation Study, the brain child of a great educator, the late President Lotus D. Coffman, erected to carry out his idea of the state-wide campus or a "University for all the people."

as to means." The Commission has given one point particular emphasis: continuation teaching must be separated "into two independent categories which should be clearly differentiated; namely, instruction to general practitioners and to qualified specialists."

Inasmuch as approximately 80 per cent of all pregnant women are delivered by general practitioners, it is evident that we, as obstetricians, owe an especial obligation to them to provide continuation study courses if we are to keep the general level of obstetric practice abreast of progress in our field. To accomplish this, every state within the area of this Association should have a state society of obstetrics and gynecology, however few the number of specialists may be. If there are any doubts about the feasibility of this suggestion, I refer doubters to the case of North Dakota, where there are only fifteen specialists in our field in the whole state and not one maternity hospital; yet the general profession looks to this little society for leadership in continuation study, and maternal and child welfare. Every state can do the same.

We see in this brief retrospect the improvements in medical education, that each phase was due to a challenge to the medical educators and the profession by some weakness or advancement of science, requiring change in pedagogic methods, and that the challenge has been met courageously and with sound judgment.

We have faith that the same courage and judgment will ultimately lead to a solution of the difficult problems of postgraduate study in the midst of which we are now struggling. It is encouraging to note that the meager beginnings of twenty years ago have grown to the stature of a movement. When the problems are thoroughly understood, and all motivating forces mutually attack them, the solution of the sixth phase, continuation study, will be on its way, just as the previous five phases were solved by conjoint effort.

The Commission, realizing the educational difficulties, states:

"Because graduate medical education is so new and has been growing so rapidly, there is no clear definition of its content and no accepted standards of its quality and length. . . . Therefore, there are several outstanding needs in this field. First, there is the need of a clear definition of postgraduate work for general practitioners and specialists. Second, to provide more opportunities for proper postgraduate education for each group. Third, to convince some physicians of the need for continued education.

"Postgraduate medical education may be applied to any type of systematic, supervised educational activity that helps the physician keep abreast of the developments in his field of practice, but not designed to qualify him to enter a new field (or specialty).

"While some courses offer material of true educational value, others have been either too superficial or too technical.

"There is real need, therefore, for the development of standards of educational content. Because of the newness of the field, standards have heretofore been impossible. But broad educational standards can and should now be developed."

It is evident that the Commission, while approving the experiments, is at the same time concerned about their educational value and about the type of teaching which, self-evidently, must come largely from the medical schools.

We have observed how the discoveries of science during the last half century, greater than during all the preceding centuries, have forced medical education to change through six rather definite phases.

Medical educators have developed a philosophy and methods which approach, more and more, a solution of the first five phases. We may fairly assume that problems of the sixth phase, postgraduate education, may be elucidated by the same sound pedagogic philosophy. However, solutions will not be made by "rule of thumb." Much experimentation must be undertaken.

Many plans have been proposed with some good in all of them, but with drawbacks in most of them. Their very number is at once their strength and their weakness. The numerous plans are an evidence of strength evincing a widespread interest. Their weakness lies in the fact that some of them are pedagogically unsound.

Self-evidently the problem is to find the strength and to eliminate the weakness. For these reasons, there should be wide discussion, especially by the special obstetric and gynecologic societies like this one. Medical schools inevitably should lead; perhaps by the organization of departments of postgraduate education with a full-time director. Mutual efforts by all agencies, medical schools and societies, and departments of health are the key and the final goal for the solution. While all plausible ideas should be tried, they must be critically analyzed in order that they may be proved educationally sound.

Postgraduate education should be developed so completely that it may be made available to the whole profession. To this end I suggest that this society, in order that it may do its full part, organize a symposium in which all the apparently sound methods may be presented by their supporters and discussed by all, with the hope that the soundest plans may be determined.

The building is designed to offer a place for continuation study in any department of the University. It contains lecture, study, and seminar rooms, a chapel (used also for lectures), library, lounge, dining room, hotel rooms with bath, where any one attending courses may live alone or with his wife. There is a large basement garage where one may park his car at a small fee during his entire period of continuation study. In short, it offers all the facilities of a fine club in the scholastic environment of a great university. The earnest attitude of the Medical School toward continuation study is attested by the fact that, in 1936, it established a department continuation study under the direction of a full-time director, Dr. William A. O'Brien.

In addition to knowledge attained from a large, high-class faculty, there is the advantage of constant, informal discussion with other practitioners enrolled in the courses. Instead of a few hours of instruction at home, which is subject to interruption by professional calls at all times, courses at the Center afford little interference.

The courses vary from twenty-one hours for three days to thirty-six hours for six days. In the three-day courses the evenings are occupied by teaching. In the six-day courses the evenings are free. The cost of the courses is \$2.75 a day for room and meals, and the tuition is \$15.00 for three days and \$25.00 for six days. There are no extra expenses. A unique feature in the Minnesota plan is that the courses in obstetrics and pediatrics, which are usually given conjointly, cost the out-of-town physician nothing. Expenses are paid by the Minnesota Department of Public Health from funds received by provisions of the Social Security Act. Any Minnesota county medical society may select one (occasionally more) of its members to attend the courses. The physician advances the costs and the Department of Health reimburses him. It is understood that he shall give a report of proceedings to his society, which is made easy for him by a complete mimeographed, bound copy of all lectures. These men attend, not for their own benefit alone, but they are also emissaries from their societies and return as missionaries of up-to-date obstetrics, gynecology, and pediatrics. Therefore, the benefit is state-wide and more, because county societies of North and South Dakota, under the identical plan, send representatives to the Center.

In 1939 to 1940, 129 physicians from Minnesota availed themselves of these opportunities; 72 enrolled from North Dakota and 30 from South Dakota. When we reflect that these 221 physicians from three states taking the courses in one year represent a society membership close to 3,000 physicians, the educational influence of this one Center of continuation study is indeed extensive.

However, we do not offer the Minnesota plan as a solution of the problems of continuation study. We are very critical and all who cooperate in the project still consider it an experiment. But I should like to add that whatever has been accomplished was possible only through the heartiest cooperation of all the agencies interested in continuation study: the Minnesota State Medical Association, the Minnesota Society of Obstetrics and Gynecology, the University of Minnesota Medical School, and the Minnesota Department of Public Health.

attempting to predict the present expected nursing course of any mother on the basis of her previous nursing record, we found that our highest percentage of correct predictions was among mothers with the so-called good nursing background. Only mothers who meet the three following conditions can be considered to have a good nursing history and can be expected to feed the baby entirely from breast during the present confinement: (1) the last baby was nursed entirely from breast for a period of at least two months; (2) the age of the patient is less than 35 years; (3) the date of the last confinement does not exceed three years. Predictions of the present nursing course among mothers with a poor nursing record are less reliable. We selected for this group only those with a history of the baby having been removed from breast early in the post partum because of insufficient milk secretion.

Stilbestrol was administered orally to 29 nursing mothers beginning the first post-partum day. There were 23 mothers with good and 6 mothers with poor nursing histories. Since we were interested in establishing a deficiency of lactation by the fifth post-partum day, the total dose of stilbestrol given and the number of days over which it was given varied greatly from case to case. The lowest daily dose was 5 mg., the highest was 15 mg. The total dose ranged from 10 mg. over a two-day period as a minimum to 50 mg. over a four-day period as a maximum.

The nursing background was not considered in the selection of the 23 mothers who received stilbestrol beginning the sixth post-partum day. Primiparas as well as multiparas were used, the only requirement being that these mothers were secreting sufficient breast milk on the fifth post-partum day for full-breast nursing. The daily dose varied from 5 mg. to 20 mg. The minimum total dose was 10 mg. during a two-day period, while the maximum was 60 mg. over a four-day period.

There were 15 patients who received testosterone early in the puerperium. The dose in all cases was uniform. Beginning at 9:00 P.M. on the first post-partum day, 25 mg. of testosterone were given intramuscularly. At 9:00 A.M. and 9:00 P.M. on the second and third days, 25 mg. were administered for a total dose of 125 mg.

Ten mothers nursing their babies full breast on the fifth day were given testosterone beginning at 9:00 A.M. on the sixth day. The injections were repeated every twelve hours until a total of 125 mg. had been administered.

Five mothers received injections of theelin beginning at 9:00 P.M. the first post-partum day. Each dose contained 50,000 international units and was given at twelve-hour intervals for a total of 250,000 units.

Five mothers nursing their babies full breast on the fifth day received 50,000 international units of theelin at 9:00 A.M. on the sixth day. Doses were administered every twelve hours until a total of 250,000 units had been given.

DATA

Stilbestrol, early post partum.—Six mothers with good nursing histories, who received 15 mg. to 35 mg. of stilbestrol early, secreted sufficient breast milk on the fifth and twelfth days for full-breast nursing. All of them showed some fullness of the breasts as milk secretion increased, but they were free of conspicuous breast engorgement characterized by distention and discomfort.

Six mothers with good nursing histories, who received 15 mg. to 50 mg. of stilbestrol early, were limited to part-time breast nursing by the fifth post-partum day. All six increased to full-time nursing by the tenth day. The breasts were quite soft during the first five days and showed only slight fullness as milk production increased. Breast distention and discomfort were absent throughout the ten-day period.

Among 23 mothers with good nursing histories, we were able to establish a deficiency of lactation on the fifth day in only 11. It is interesting that 8 of these 11 were nursing their babies full-breast on discharge from the hospital the tenth post-partum day. Two patients increased from a deficiency of lactation to part-time nursing, while one baby was taken off breast at the request of the mother

INHIBITION OF LACTATION*

H. L. STEWART, JR., M.D.,† AND J. P. PRATT, M.D.,
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(From the Department of Obstetrics and Gynecology, Henry Ford Hospital)

STILBESTROL, testosterone, and theelin have been reputed to be inhibitors of human breast secretion. For the most part, the reports assumed that breast engorgement was synonymous with breast secretion. During a study of normal lactation among 900 consecutive nursing mothers, we observed that the degree of early breast engorgement does not consistently indicate the amount of subsequent milk production. Frequently mothers with conspicuous breast distention and discomfort fail to secrete sufficient breast milk and must rely upon complementary feedings within a few days. In distinct contrast, a mother who passes through the engorgement stage in relative comfort may secrete sufficient milk for full-breast nursing. These observations have stimulated critical analysis of inhibition of lactation. We were interested in determining whether inhibition of breast engorgement is synonymous with inhibition of lactation. Other questions that arise are: What is the effect on breast secretion when stilbestrol, testosterone, or theelin is administered early in the post-partum period? If these hormones inhibit breast secretion, is the effect temporary or permanent? Will these hormones inhibit breast secretion after lactation is established and is the effect temporary or permanent?

METHOD

All babies in this study nursed alternate breasts every four hours beginning twelve hours after delivery. Water was administered during the first forty-eight hours as necessary; thereafter, complementary formula feedings were used as indicated. The babies were weighed before and after each nursing, and the total daily milk secretion was carefully recorded. All mothers were classified on the fifth and tenth post-partum days on the basis of a total twenty-four-hour milk secretion and assigned to one of three groups: full-breast, part-time, or deficient nursing. (The method of classification has been previously reported in detail.¹) If the milk secretion was insufficient for full-breast nursing on the fifth post-partum day, the breast was emptied with an electric breast pump after each nursing. Pumping the residual milk is necessary to determine whether the baby is completely emptying the breasts at each nursing, for cases of apparent deficiency oftentimes are secreting sufficient milk to be classed as part time or full-breast nursing.

All patients receiving stilbestrol, theelin, or testosterone early in the post-partum period were carefully selected on the basis of their previous nursing record. Only mothers with good or poor records were used. Our standards of a good nursing history were based on a study of the records of 900 nursing mothers. In

*Read at the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

†Dr. Stewart is now in the Department of Obstetrics and Gynecology, Temple Medical School, Philadelphia, Pa.

on the eighth post-partum day. In all of these mothers the breasts on the fifth day were soft, and breast engorgement was not encountered during the subsequent five days in the hospital.

Six mothers with poor nursing histories, who received 10 mg. to 30 mg. of stilbestrol early, remained deficient on the fifth day, and only one of them increased to part-time nursing on the tenth day.

Stilbestrol, After Fifth Post-Partum Day.—As tabulated in Table II only 3 of the 23 mothers nursing their babies full breast on the fifth day were reduced to part-time nursing by the tenth day. In no case were we able to inhibit lactation to a state of deficiency. It is true that 10 of 23 mothers showed less milk secretion on the tenth post-partum day as compared with the fifth post-partum day, but the fall in milk production in 7 of these mothers was not sufficient to interfere with continuation of full-breast nursing. We noted no constant relation between the amount of stilbestrol given and the decline in milk secretion.

Relatively larger doses of stilbestrol were given in this part of the study. Once lactation is established, the effect of stilbestrol is much less than when it is administered before lactation is established.

TABLE III

TESTOSTERONE ADMINISTERED EARLY POST PARTUM	
Nursing on Fifth Post-Partum Day	
Full-breast nursing	13 cases
Part-time nursing	2 cases
Deficient nursing	No cases
Nursing on Tenth Post-Partum Day	
Full-breast nursing	14 cases
Part-time nursing	1 case
Deficient nursing	No cases
TESTOSTERONE ADMINISTERED AFTER FIFTH POST-PARTUM DAY (All Patients Full-Breast Nursing on Fifth Day)	
Nursing on Tenth Post-Partum Day	
Full-breast nursing	10 cases
Part-time nursing	No cases
Deficient nursing	No cases

Testosterone.—Table III shows that 13 of 15 mothers, each receiving 125 mg. of testosterone early in the post-partum period, were nursing their babies full breast by the fifth day. Two were part-time nursing. A deficiency of lactation was not established with 125 mg. of testosterone.

TABLE IV

THEELIN ADMINISTERED EARLY POST PARTUM	
Nursing on Fifth Post-Partum Day	
Full-breast nursing	5 cases
Part-time nursing	No cases
Deficient nursing	No cases
Nursing on Tenth Post-Partum Day	
Full-breast nursing	5 cases
Part-time nursing	No cases
Deficient nursing	No cases
THEELIN ADMINISTERED AFTER FIFTH POST-PARTUM DAY (All Patients Full-Breast Nursing on Fifth Day)	
Nursing on Tenth Post-Partum Day	
Full-breast nursing	5 cases
Part-time nursing	No cases
Deficient nursing	No cases

TABLE I. SUMMARY OF PATIENTS ADMINISTERED STILBESTROL EARLY IN POST-PARTUM PERIOD

CASE	NURSING HISTORY	POST-PARTUM DAYS STILBESTROL GIVEN	TOTAL DOSE MG.	TYPE OF NURSING	
				5TH DAY	10TH DAY
8	Good	1st through 5th	35	Full	Full breast
10	Good	1st through 5th	30	Full	Full breast
24	Good	1st through 3rd	30	Full	Full breast
9	Good	1st through 4th	30	Full	Full breast
28	Good	1st through 5th	25	Full	Full breast
2	Good	1st through 3rd	15	Full	Full breast
15	Good	1st through 4th	50	Part time	Full breast
16	Good	1st through 3rd	30	Part time	Full breast
19	Good	1st through 3rd	30	Part time	Full breast
29	Good	1st through 3rd	30	Part time	Full breast
4	Good	1st through 3rd	15	Part time	Full breast
5	Good	1st through 3rd	15	Part time	Full breast
25	Good	1st through 4th	40	Deficient	Full breast
27	Good	1st through 4th	35	Deficient	Full breast
12	Good	1st through 3rd	30	Deficient	Full breast
20	Good	1st through 3rd	30	Deficient	Full breast
22	Good	1st through 3rd	30	Deficient	Full breast
23	Good	1st through 3rd	30	Deficient	Full breast
7	Good	1st through 4th	25	Deficient	Full breast
11	Good	1st and 2nd	20	Deficient	Full breast
6	Good	1st through 3rd	15	Deficient	Part time
14	Good	1st through 3rd	30	Deficient	Part time
18	Good	1st through 4th	40	Deficient	Off breast
21	Poor	1st through 3rd	30	Deficient	Deficient
17	Poor	1st through 4th	25	Deficient	Part time
1	Poor	1st through 3rd	15	Deficient	Deficient
3	Poor	1st through 3rd	15	Deficient	Deficient
13	Poor	1st through 3rd	15	Deficient	Deficient
26	Poor	1st and 2nd	10	Deficient	Deficient

TABLE II. PATIENTS ADMINISTERED STILBESTROL AFTER THE FIFTH POST-PARTUM DAY
(All Patients Full-Breast Nursing on the Fifth Day)

CASE	TOTAL DOSE ADMINISTERED MG.	NURSING 10TH DAY	DROP IN MILK SECRETION BY 10TH DAY
1	10	Full breast	0
2	10	Full breast	0
3	20	Full breast	0
4	20	Full breast	0
5	20	Part time	55 c.c.
6	35	Full breast	0
7	20	Full breast	0
8	20	Part time	160 c.c.
9	30	Full breast	5 c.c.
10	30	Full breast	0
11	30	Full breast	0
12	40	Full breast	0
13	45	Full breast	5 c.c.
14	40	Full breast	100 c.c.
15	40	Full breast	0
16	40	Part time	105 c.c.
17	60	Full breast	50 c.c.
18	60	Full breast	50 c.c.
19	50	Full breast	120 c.c.
20	50	Full breast	100 c.c.
21	50	Full breast	0
22	50	Full breast	0
23	60	Full breast	0

Illustrated graphically in Chart 1 is a curve of daily milk secretion which is typical of the group receiving theelin early post partum. As shown by this curve, most of the mothers had a slight inhibition of lactation either on the second or the third post-partum day. This "plateau effect" is the only difference in the theelin patients as compared with those receiving testosterone. The lactation curves of those receiving theelin or testosterone after the fifth day are similar.

DISCUSSION

From the data presented in Table I, we note that patients with a good nursing background, receiving stilbestrol early in the lactation period, vary from a deficiency to full-breast nursing by the fifth post-partum day. On account of individual variation in the response to the drug, one cannot predict whether stilbestrol will cause a temporary inhibition of lactation. A dose of 15 mg. for one patient (Case 6) was sufficient to

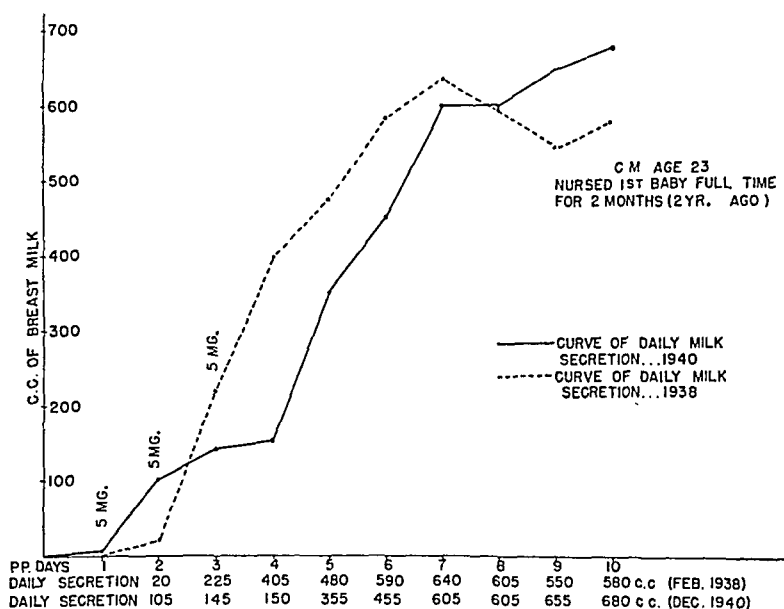


Chart 3.

establish a deficiency of lactation by the fifth day, while another patient (Case 8) who received 35 mg. was nursing her baby full breast on the fifth day. Individual response to the drug is important in determining the degree of milk suppression.

Breast engorgement was absent in all cases regardless of the variable individual response in milk production when stilbestrol was administered early. Breast fullness was more noticeable in mothers nursing their babies full breast on the fifth day than in mothers with part-time or deficient nursing, yet none had manifest breast engorgement so vividly remembered from previous pregnancies. These observations signify that absence of breast engorgement is not a good indicator of subsequent milk production and that inhibition of engorgement is not synonymous with inhibition of lactation.

Chart 2 presents a typical lactation curve for the 6 mothers receiving stilbestrol early post-partum with sufficient breast milk for full-breast nursing on the fifth post-partum day. The amount of the drug and the dates of administration are

In comparison with mothers receiving stilbestrol early, breast distention and fullness were greater in the testosterone group. No mother complained of discomfort, and conspicuous breast engorgement was absent.

On the tenth day 14 mothers were secreting sufficient milk for full-breast nursing, one of whom nursing part time on the fifth day increased to full-time nursing.

Ten mothers who received 125 mg. of testosterone after the fifth day were nursing their babies completely from the breast by the tenth day. Only 2 mothers showed less milk secretion on the tenth day as compared with the fifth day. In the first and tenth patients (Cases 1 and 10) the milk decline was 145 c.c. and 65 c.c., respectively.

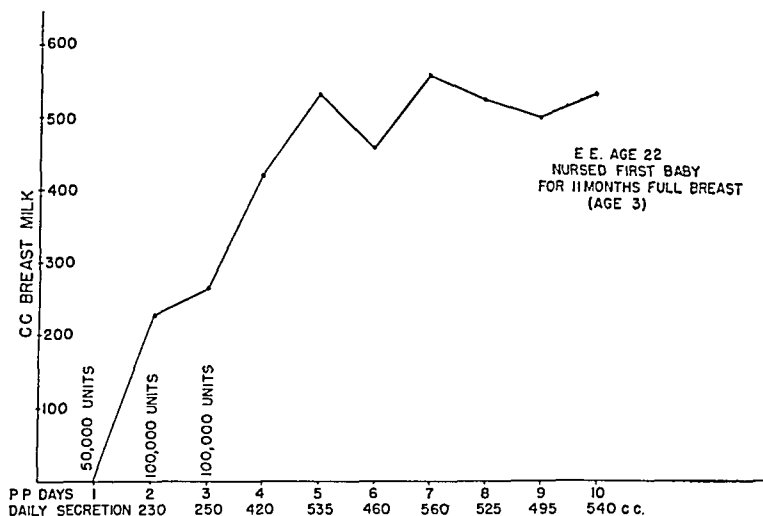


Chart 1.

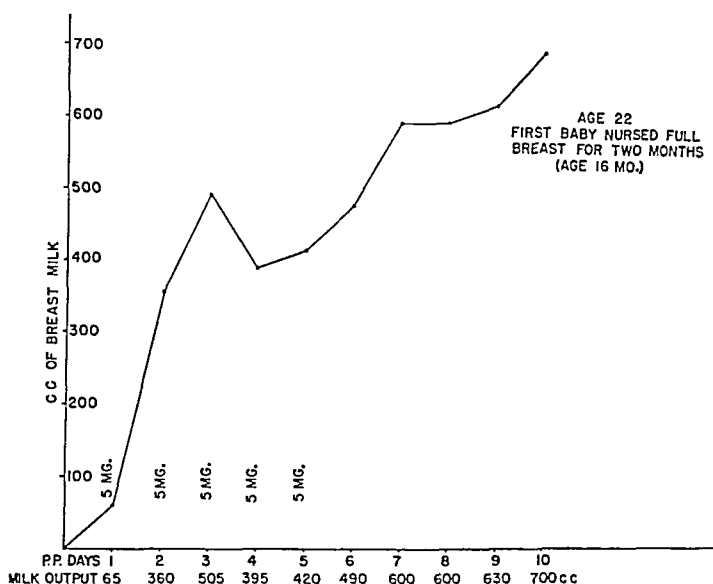


Chart 2.

Theelin.—In the small series of 10 patients receiving theelin, 5 were in the early post-partum and 5 in the late post-partum period. Each received 250,000 international units of theelin. The incidence of full-breast nursing was not affected whether theelin was administered early or late in the post-partum period. As in the testosterone series, the breasts were full but engorgement was not encountered.

output. If the milk secretion on the sixth day is approximately twice that of the fifth, and the seventh day is twice that of the sixth, full-breast nursing may be predicted with confidence. All deficiency cases discharged on the tenth day with full-breast nursing show this characteristic rise after the stilbestrol has been discontinued for forty-eight hours.

The temporary deficiency due to depression of secretion by stilbestrol may be contrasted with true deficiency in the control. Among 900 consecutive nursing mothers none of those with deficient lactation on the fifth day were discharged with full-breast nursing on the tenth day.

Chart 5 shows a deficiency curve characteristic for 6 mothers with a poor nursing background. A deficiency curve obtained from the same patient in 1938 (without stilbestrol) is presented for comparison. On the basis of a comparative study of lactation curves in the deficiency group, we found that stilbestrol will further inhibit, but not completely suppress, lactation. Patients with poor or

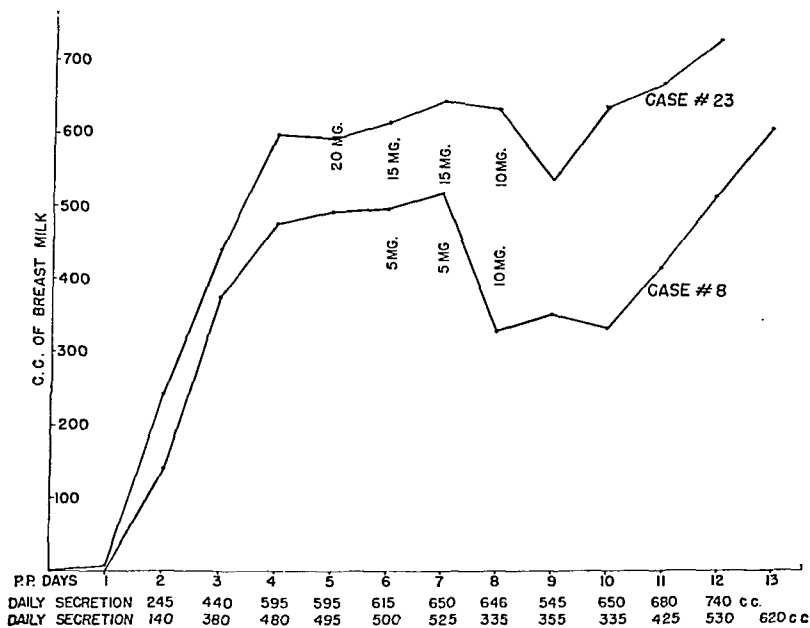


Chart 6.

deficient nursing records are not suitable for a study of inhibition of lactation. While all those receiving stilbestrol will show absence of breast engorgement, deficiency of lactation on the fifth day, and absence of rise to full-breast nursing by the tenth day, many patients will show the same without the administration of stilbestrol.

When stilbestrol was administered after the fifth day to full-breast nursing mothers, it was not possible to reduce milk secretion to a deficiency level in any case. It was not possible to decrease milk secretion in all cases. The amount of decline was not proportional to the dose administered.

The curve of Case 8 is presented in Chart 6 to show the most marked drop in this series. The temporary effect lasting for forty-eight hours was followed by a rapid secondary rise. In the same chart is the curve of Case 23. This mother received three times the dose of stilbestrol given to Case 8, but presented only a minor change in the curve of secretion. A comparison of these two curves serves to illustrate our observation that the lower the curve of full-breast secretion, the less is the dose of stilbestrol required to depress the lactation curve. The amount of diminished secretion varies greatly with the individual case.

It is our opinion that testosterone and theelin inhibit breast engorgement. When either of these substances is administered early or

shown. There is a rapid rise in milk secretion the first three days. A definite fall the fourth day is in contrast with the "plateau effect" in the theelin curve of Chart 1. With the secondary rise in milk secretion after the fifth day, breast fullness increases without engorgement.

Chart 3 illustrates the type of curve obtained from the 6 mothers with part-time nursing on the fifth day. Previous nursing records serve as control for comparison. This chart shows the average daily secretion of breast milk during a previous as well as a recent admission. Stilbestrol delays the rise in the lactation curve temporarily, but the effect disappears rapidly after the medication is stopped.

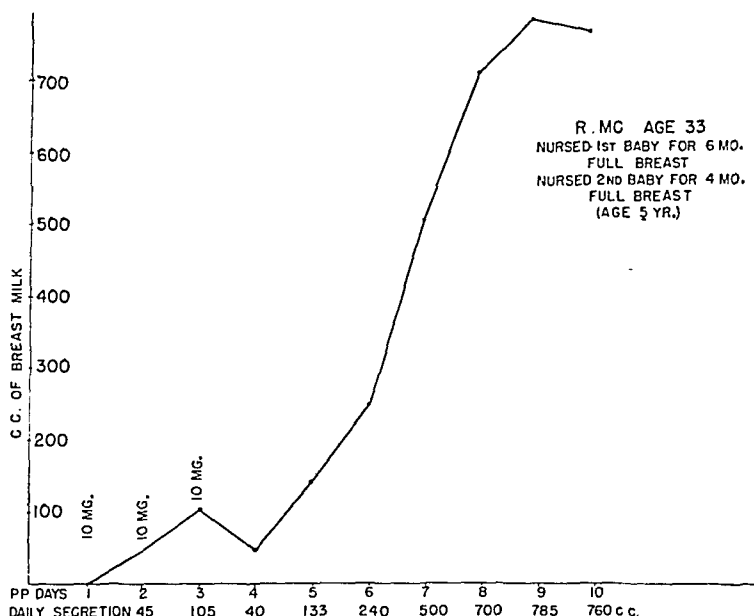


Chart 4.

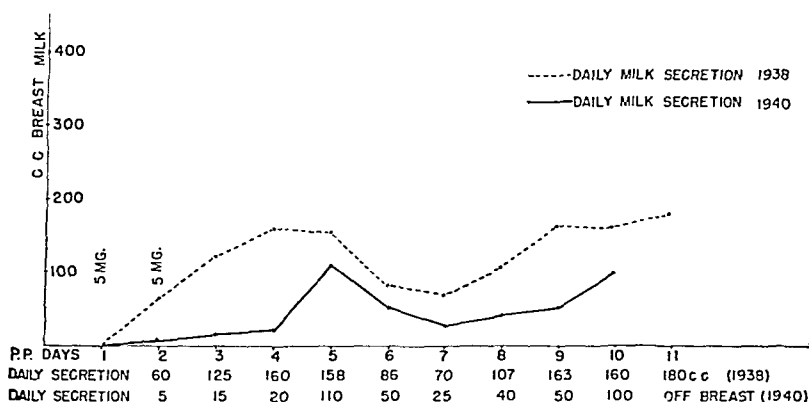


Chart 5.

Chart 4 shows a curve typical for the group of 8 mothers in which a deficiency of lactation was established temporarily with stilbestrol. The curve was taken from a patient who presented an excellent nursing background. The absence of engorgement on the third day alarmed her because she feared this was an indication of permanent insufficiency of milk to feed the baby. She was soon reassured by the characteristic rise in milk after the drug was discontinued. Most mothers showed no increase in milk secretion for forty-eight hours after the stilbestrol was discontinued (third to fifth days). The patients who will be discharged with full-breast nursing can be predicted on the basis of the sixth and seventh day

Administration of stilbestrol gave interesting results. Twelve of 23 primiparas, who received 5 mg. of stilbestrol in a single dose the first day, had no engorgement or pain in the breasts, while 8 others had some discomfort for a few hours on either the third, fourth, or fifth day. These patients, however, did not have the usual amount of engorgement associated with the period when lactation begins. Three patients showed no demonstrable effect.

Twenty of 27 multiparas receiving stilbestrol gave a satisfactory nursing background. Fourteen of these women received 5 mg. of the drug the first day post partum; 4 had mild engorgement of the breasts on either the fourth or fifth day, while the breasts of the remaining 10 remained soft. Ten milligrams of stilbestrol were given to 4 patients on the first post-partum day; 3 had some lactation but no engorgement; the fourth showed no effect. Three mothers, who had chronic engorgement of the breasts associated with pain due to excessive lactation, were given repeated doses of 10 mg. each until they received a total of 20 to 30 mg. In 3 mothers the breasts became soft, but continued to lactate; in the fourth, lactation was inhibited so that there was insufficient milk for the infant, but by stopping treatment the milk supply gradually came back to normal within three days. This effect was also observed in 2 other mothers who received a single dose.

Since only one in 50 patients had clinically a toxic reaction (nausea), it is apparent that stilbestrol produces toxic reactions in fewer post-partum patients than in nonpregnant patients. Inhibition of breast engorgement was obtained in many mothers with relatively small doses of stilbestrol provided the drug was given the first day post partum. Many of these individuals continued to lactate for several days. On the other hand, although our observations are inadequate, we are inclined to agree with Dr. Pratt that some inhibition of lactation is possible even when the mother is nursing the baby. The impression is gained that inhibition of breast engorgement is not synonymous with inhibition of lactation.

DR. HERBERT E. SCHMITZ, Chicago, Ill.—In a recent publication I gave our results of the study of involution in those patients receiving oxytocics. Certain of these patients were unwed mothers at St. Vincent's Hospital, and they received 1 mg. of stilbestrol daily for from three to six days in order to control engorgement of the breasts. It was our observation that involution was delayed in these patients. I wonder whether Dr. Pratt has made the same observation.

DR. H. CLOSE HESSELTINE, Chicago, Ill.—Dr. Pratt and Dr. Stewart have pointed out very clearly the necessity for adequate controls and have made strenuous efforts to keep the study balanced. Many factors affect lactation. It varies even in the same individual in different pregnancies but otherwise under the same circumstances. Such factors make proper controls necessary.

Dr. M. Edward Davis and his colleagues, Dr. Louis Clancy and Dr. Simon Wolters, have a similar study well under way at the present time at the Chicago Lying-in Hospital. He and Dr. Clancy have studied 140 patients in whom they attempted to relieve engorgement or to suppress lactation by giving stilbestrol 5 mg. daily for a total of 25 to 50 mg. Of this number, two-thirds were multiparas and one-third were primiparas. The great majority of them were patients at or near term. The indications for therapy were found in patients who could not nurse because of stillbirths, active pulmonary tuberculosis, inadequate lactation or nipple and breast lesions, etc.

The findings at the Lying-in Hospital agree in general with what Dr. Stewart and Dr. Pratt report. Dr. Clancy found a great variation in the degree of suppression with most patients having a distinct inhibition of lactation, but practically all had some expressible secretion at the end of ten days. Their observations indicate that it was much easier to prevent the initial engorgement of the breasts by the early administration of stilbestrol than it was to suppress lactation once lactation had been established. Dr. Wolters administered the same amount of stilbestrol preparation for five to eight days to 15 nursing multiparas. Partial and complete suppression occurred in many, but 7 had sufficient milk for the baby on the discharge date. Thus, Dr. Davis and his colleagues demonstrate complete lactational inhibition in some, while others lactate adequately under the stimulation of

late in the post-partum period, the effect on the milk secretion is negligible. There is a slight alteration in the rise of milk secretion when theelin is given early, while no effect is noted with testosterone. This is illustrated in Chart 1.

We found it necessary to discontinue stilbestrol in 2 patients because of nausea. In no case did vomiting follow the administration of this drug. The lochia remained normal in all patients during the hospitalization period. Three persons of the stilbestrol and 2 of the testosterone series reported that the lochial flow increased within a few days after discharge from the hospital.

CONCLUSIONS

Inhibition of breast engorgement is not synonymous with inhibition of lactation.

Engorgement of breasts may be prevented by suitable doses of stilbestrol, theelin, or testosterone.

Lactation may be diminished temporarily by stilbestrol, but the individual response varies widely.

The effect of 250,000 international units of theelin and 125 mg. of testosterone on lactation is negligible.

We wish to express our appreciation to E. R. Squibb and Sons for their generous supply of stilbestrol; to Parke, Davis & Co. for theelin, and to the Schering Corporation for testosterone. We also wish to express our appreciation for the assistance of Miss Hitchingham and her assistants for weight records.

REFERENCE

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712 CASS AVENUE.

DISCUSSION

DR. A. W. DIDDLE, Iowa City, Iowa.—Our interest at the University Hospitals has been primarily in the action of stilbestrol and testosterone propionate on breast engorgement and to a lesser degree in the effect of the former on breast secretion after lactation has been established.

Results are available on 60 mothers, ranging in age from 17 to 39 years. Fifty-four of these neither nursed their babies nor had their breasts pumped, while 6 fed their newborn on alternate breasts every four hours. Twenty-five patients were primiparas and 35 were multiparas. Ten mothers received 25 mg. of testosterone propionate every other day until a total of 75 mg. were administered, beginning on the second post-partum day. Stilbestrol was given to 50 women. Forty received the drug within the first twenty-four hours, 35 of the 40 being given 5 mg., and the other 5, 10 mg. in a single dose. Five patients received 5 or 10 mg. of stilbestrol on the second day post partum, while 4 others were given larger doses—10 mg. every day for two or three days. Another patient received two doses of 5 mg. each in one day, two months post partum for inhibition of lactation.

Observations were made for purposes of comparison on 60 post-partum women who received no treatment and who never nursed their babies. In this group breast engorgement was noted on the second to fifth post-partum day, but it usually occurred on the third day. Only 2 had no distention or tenderness of the breasts. The duration of congestion ranged from eighteen to seventy-two hours, with the average range twenty-four to thirty-six hours.

Those patients who were treated with testosterone had symptoms comparable to the untreated group. The drug had no apparent effect.

enough sulfanilamide to have her excrete a therapeutic dose of the drug in her milk. It is probable that the excretion of stilbestrol is in the same proportion.

Opinions concerning the toxicity of stilbestrol vary widely. In a large number of patients that we have studied for their reaction to stilbestrol, we have found a relatively low toxicity in pregnant as well as in nonpregnant women. In none of the pregnant women studied was it necessary to discontinue the preparations on account of toxicity. Among the nonpregnant women we noted about 4 to 8 per cent responded unfavorably. Critical analysis of all the circumstances reduces the number that appear to have toxic reactions. One woman who may have been classed as manifesting toxic symptoms had been receiving stilbestrol for several months. She left the city for six weeks, carrying a supply of the preparation with her. During her absence she developed a gall bladder attack, with nausea and vomiting and epigastric distress. She took the stilbestrol regularly when not vomiting and continued to take it until she reported later. The acute attack ran the usual course and was apparently not influenced by the medication. Had she begun to take stilbestrol coincident with the onset of the gall bladder attack, the vomiting would probably have been attributed to the medication. In contrast to this case we may cite the experience of a woman who was nauseated the first day she took stilbestrol and vomited the second day. She discontinued the drug on her own initiative. Later she was given a placebo which produced no symptoms. A second attempt to use stilbestrol gave the same result as on the first occasion. This patient should unquestionably be classed as toxic. Only about 4 per cent of our cases gave this experience. In all instances they stop the medication voluntarily. We have found no harmful effect from the use of stilbestrol.

I appreciate what Dr. Taussig said about variables and heartily agree that we must have numerous observations. If he will reflect for a moment he will realize that it takes considerable time and effort to get 900 controls. Even this number does not justify final conclusions, but it should show the trend. We feel that this number of observations justifies a report at this time and hope that others will contribute their experience with controlled experiments. Isolated cases selected at random do not furnish a satisfactory basis for drawing conclusions. Adequate controls are necessary.

BLOOD PROTHROMBIN LEVELS IN THE NEWBORN*

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INDIANAPOLIS, IND.

(From the Department of Obstetrics, Indiana University Medical Center)

THE demonstration by Dam and Schönheyder¹ in Denmark (1934) and by Almquist and Stockstad² in this country of an antihemorrhagic vitamin has resulted in widespread investigations. Dam named this substance vitamin K. In 1936 Dam, Schönheyder, and Tage-Hansen,³ and subsequently Quick,⁴ demonstrated a relationship between vitamin K and the prothrombin level of the blood, and the latter suggested that man might suffer from faulty absorption of vitamin K because of the lack of bile in the intestine. Warner, Brinkhous, and Smith,⁵ and immediately thereafter Butt, Snell, and Osterberg,⁶ demonstrated the value of vitamin K and bile in the bleeding tendency of obstructive jaundice. Continued investigation⁷⁻⁹ has verified the importance of vitamin K in the establishment and maintenance of adequate prothrombin levels in the blood.

*Prize Award Essay, Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

This study has been aided by a grant from the Landon Research Fund of the Indiana University Medical Center.

nursing or immediately after the withdrawal of stilbestrol. Moreover, they made the interesting observation that puerperal patients tolerate this larger dosage better than others, for there were no instances of nausea and vomiting.

DR. KARL JOHN KARNAKY, Houston, Texas.—On our obstetric service at the Jefferson Davis Hospital in Houston, we found one baby who developed diarrhea while we were giving stilbestrol to the mother. When we took the mother off the drug, the baby returned to normal. However, this is only one case, and we have had 20 delivered patients in all to whom we gave 5.0 mg. of stilbestrol for twenty days. We found the babies were able to nurse the same as if the mothers were not receiving stilbestrol.

We have investigated the alleged toxicity of stilbestrol in great detail. We completed 2,058 laboratory tests on 426 charity patients over the course of fifteen months. We gave doses varying from 3.5 mg. up to as high as 36,000 mg. I have published an article in the September, 1940, issue of the *Texas State Medical Journal* proving that stilbestrol is not toxic. I am fortunate to be able to keep patients in the hospital as long as I desire, or until they are taking about as much stilbestrol as necessary. Still they are not sick nor do any changes take place in their blood chemistry.

One patient was receiving 254 mg. of stilbestrol when she was accidentally killed. From the autopsy I have all the tissues and these show no changes in the kidney, liver, or other organs.

I now give 25.0 to 100 mg. of stilbestrol intramuscularly to every patient who has uterine bleeding and who comes to our charity hospital.

I have at present one woman who has taken over a course of fifteen months 36,000 mg. of stilbestrol. Her initial dose was 0.1 mg. every day and this has been increased until she gets 100.0 mg. every day by mouth and 200 to 5,000 mg. intramuscularly once or twice a week. She has had a complete blood chemistry every two to three weeks.

We have treated in all more than 1,100 patients with stilbestrol. We have observed that when we give 5 mg. the first night, the patient has nausea the next morning, but if she takes another 5 mg. the next night she is 50 per cent less sick than on the first morning. The 5 mg. of the third night only gives about 25 per cent of the sick feeling of the first morning. After the fourth or fifth 5 mg. tablet, these patients are no longer ill and can take 5 mg. tablets, one every night, for twenty to sixty nights.

DR. FRED J. TAUSSIG, St. Louis, Mo.—May I just say a word about experimental methods. When we have a problem that we wish to study we should, as far as possible, try to reduce the number of variables. Furthermore, we should wait until we have a sufficiently large number of cases to justify drawing conclusions. In the third place, control experiments should, whenever possible, be employed.

For these reasons, it seems to me that if Dr. Pratt and his co-workers had limited their experiments to *one* organic compound, still retaining the variants of the previous nursing experience and the time post partum at which the medicine was employed; and if they had studied at least 100 of each of those series with two variants; and if they had also taken every other patient who came during this period of time and employed no medication whatsoever, then their conclusions would be controlled and more valuable. In judging the therapeutic result of hormonal extracts, I think we should be extremely careful to employ such controls and such larger series of experiments before coming to any conclusion.

DR. PRATT (closing).—Inasmuch as Dr. Diddle and Dr. Hesseltine agree we have no cause for argument.

Dr. Schmitz asks whether stilbestrol causes any delay in involution. We have made no day to day observations to check this relation, but the routine post-partum examinations have revealed no difference in involution between the patients who received and those who did not receive stilbestrol.

Dr. Karnaky reports the occurrence of diarrhea in a baby nursing from a mother who was receiving stilbestrol. We have experienced no similar occurrence. While we have not measured the amount of stilbestrol in mothers' milk, our experience with sulfanilamide may be cited. It is not possible to give a nursing mother

many instances daily readings were made from birth until the fifth day. Fig. 1 illustrates in per cent of normal clotting activity, the average level for each day of life in the total group. It will be noted that the average reading on the day of birth is 65 per cent of normal; this has varied from 40 to 100 per cent of normal. There is a drop during the early neonatal period which reaches the lowest level during the third twenty-four-hour period. This is followed by a rapid spontaneous rise, so that at the end of the first week of life the level of clotting activity is above that at birth.

There is, however, a wide variation in the curves of individual infants. This is illustrated by five graphs shown in Fig. 2. These were all normal full-term infants delivered without unusual incident. This marked variation is difficult of explanation. We find suggestive evidence that there is a seasonal variation in the type of curve. In 10 infants delivered during November, 1939, the average low reading was 45 per cent, while in 10 infants delivered during March, 1940, the average low reading was 12 per cent of normal clotting activity. Further study

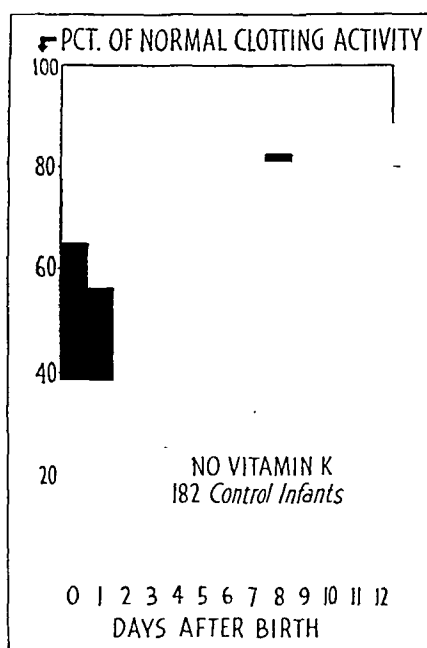


Fig. 1.—Control infants.

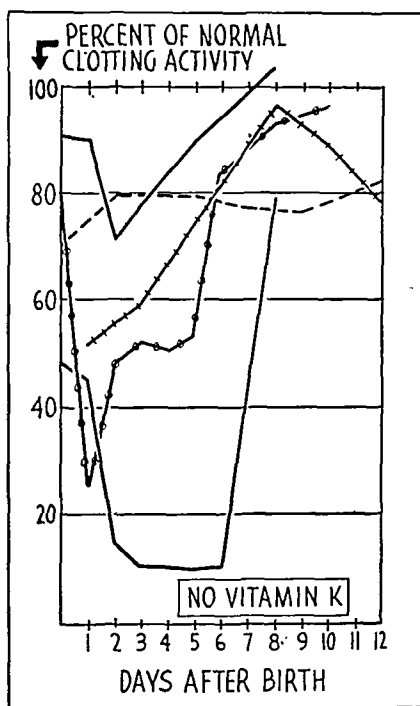


Fig. 2.—The variation in normal infants.

of this phase is being made. The observation is not surprising, however, in view of the probable difference in the diet of the average patient during the summer and winter months. We have been unable to establish any correlation between the type of curve in the infant and the level in the mother's blood. In 250 mothers tested there was none in whom a reading below 70 per cent was obtained.

In 19.7 per cent of this control group the level of clotting activity dropped below 30 per cent of normal. These marked decreases in clotting activity and the surprisingly rapid return to normal levels are illustrated in Fig. 3. Both of these infants were entirely normal as far as could be determined clinically. In several instances in this group the return to normal levels has been delayed to the seventh and eighth days without the development of untoward symptoms. One must consider such infants, however, as having a potential bleeding tendency.

During the period of the present study there have been 30 premature infants delivered. Nine of them were in the group which did not receive vitamin K. A composite curve for these infants (Fig. 4) does not indicate unusually low levels as have been reported by Hellman and Shettles,¹⁴ but confirms the observations of Kato and Poncher.¹⁶

More recent investigations have concerned the prothrombin content of the blood of newborn infants.

Brinkhous, Smith, and Warner¹⁰ reported in 1937 that the prothrombin content in the blood of newborn infants is less than 40 per cent of the adult level, and does not exceed this level during the first two weeks. It reaches the adult level at the end of the first year. In a subsequent report,¹¹ these workers describe a previously unrecognized additional drop in prothrombin level which occurs between the second and sixth days of life. They believe that a rapid convertibility of prothrombin partially compensates for the deficient quantity of prothrombin demonstrated by them throughout early infancy. Quick and Grossman¹² reported (1939) that normal levels were present in infants three days or older and that in babies six hours old the values ranged from 70 to 80 per cent of the adult normal. In two of three babies one day old, marked reduction of the prothrombin level was noted, but this low level was of short duration and spontaneously returned to normal in one or two days. Waddell and Guerrey¹³ demonstrated (1939) a marked decrease in the prothrombin level in some infants, with the greatest drop on the second and third days of life. They also demonstrated the ability of a vitamin K concentrate given orally to newborn infants in preventing this reduction. Additional reports confirming these general findings have been published during the past year by Hellman and Shettles,¹⁴ Bray and Kelley,¹⁵ and Kato and Poncher.¹⁶

Routine study of a large series of infants has been complicated by the necessity of repeated venepuncture to obtain blood for study. Recently Bray and Kelley,¹⁵ and Kato,¹⁷ have reported the use of capillary blood obtained by heel puncture as giving satisfactory results. During the past year we have been using a modification of the Smith¹⁸ bedside test reported by Smith and his co-workers¹⁸ as a simple clinical method for evaluating the prothrombin factor in the blood of the newborn infant.¹⁹

METHOD

Twenty cubic millimeters of a thromboplastin extract are placed on a clean glass slide. Blood is obtained by heel puncture from the infant to be tested. Twenty cubic millimeters of blood are immediately mixed with the drop of thromboplastin extract. The drop is pricked every second with a stylus until a firm fibrin strand adheres to the point. The interval in seconds is recorded as the prothrombin clotting time. A normal control reading is obtained in the same manner using adult finger blood. The prothrombin level is expressed in per cent of normal, using the formula suggested by Smith and co-workers:

$$\frac{\text{Clotting time of control}}{\text{Clotting time of unknown}} \times 100 = \text{Clotting activity in per cent of normal.}$$

The thromboplastin extract is prepared in the following manner: Fresh sheep or swine lung is ground and placed in a large beaker. To this is added 1 c.c. of normal saline per gram of ground lung. The lung-saline mixture is stored overnight in the refrigerator. It is then strained through a double layer of broadcloth. The saline extract is placed in small test tubes and stored in the freezing compartment of a refrigerator where it retains its potency for at least six weeks. When ready for use, a tube is allowed to thaw and is used at room temperature.

We wish to emphasize that an accurate determination of the prothrombin level in the blood is not obtained with this method. The ability of the blood to clot in the presence of an excess of thromboplastin is measured and in this way a summation of several factors is estimated, including, particularly, the amount and convertibility of prothrombin. We feel that such a test gives a satisfactory clinical assay and will indicate those infants in whom a critical deficiency of prothrombin exists.

RESULTS AND COMMENT

Control Infants.—A total of 182 infants have been studied. Determinations of the prothrombin clotting time were made at least every other day during the first ten days of life or for longer periods if the infant remained in the hospital. In

Vitamin K After Delivery.—To determine the effectiveness of vitamin K in the prevention of this observed drop in prothrombin clotting time, a vitamin K preparation (2 methyl-1, 4 naphthoquinone)²⁰ was given routinely to a series of 200 infants. The dosage employed was empirically chosen to be 1 mg. given orally in corn-oil solution 6 hours and 30 hours after birth. For purposes of evaluation it has not been changed. The composite curve obtained in this group of infants is illustrated in Fig. 5. It will be seen that the decrease in clotting activity, characteristic of the control group, is essentially absent, and the lowest level is 62 per cent. There is again a rise above the level recorded during the first day of life and a maintenance of that higher level. The slight drop which does occur during the second twenty-four-hour period may hypothetically be explained upon the basis of an insufficient dosage of the naphthoquinone until the second 1 mg. dose has been received. Further study is necessary to demonstrate such an assumption. As the vitamin K preparation was given to the infants orally and in some instances was not completely retained, this may be a factor in variations noted. Eight infants, 4 per cent of this group, showed curves decreasing to 30 per cent of normal clotting activity or below.

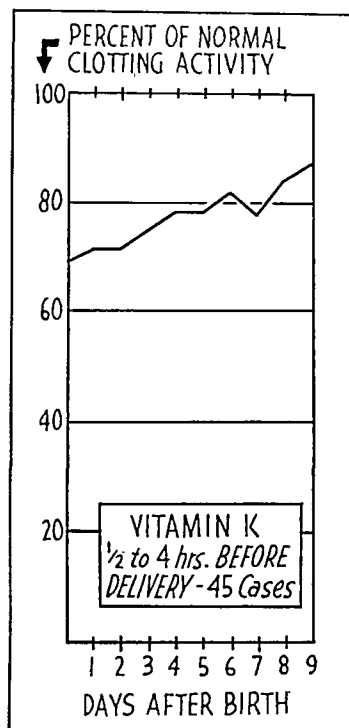


Fig. 7.—The effect of vitamin K given one-half to four hours before delivery.

Vitamin K During Labor.—The third group studied consists of 117 infants whose mothers were given the vitamin K preparation during labor. A single dose of 4 mg. of 2 methyl-1, 4 naphthoquinone in capsules was given to the patient upon admission to the labor room. Again the dosage was empirically established and was kept at a constant level. The composite curve for these infants is shown in Fig. 6. It is to be noted that no drop occurs in the clotting activity of this group. Of this group of infants 3.4 per cent showed a level of 30 per cent or less of normal clotting activity. Forty-five patients in this group received the vitamin K preparation one-half to four hours before delivery. Surprisingly the curve for this group of infants (Fig. 7) is not unlike that for the total group. Eight of these patients received the vitamin K two hours or less before delivery, and in this group the protection is incomplete but does not appear to be completely absent. It must be borne in mind, however, that some of the untreated infants show little or no drop in prothrombin clotting time, and our series is too small to

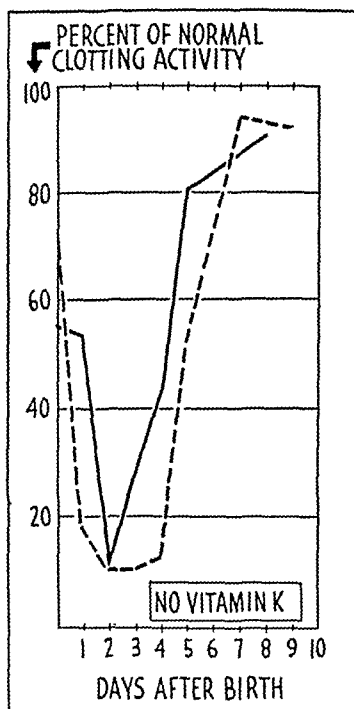


Fig. 3.

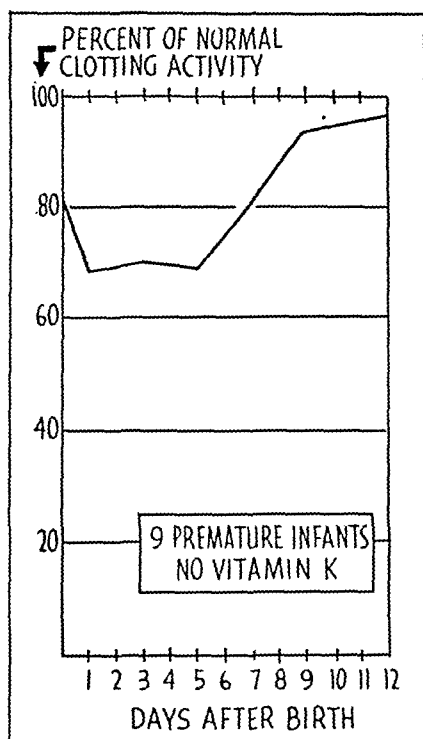


Fig. 4.

Fig. 3.—The marked drop which occurs in some normal infants.

Fig. 4.—An average curve for premature infants.

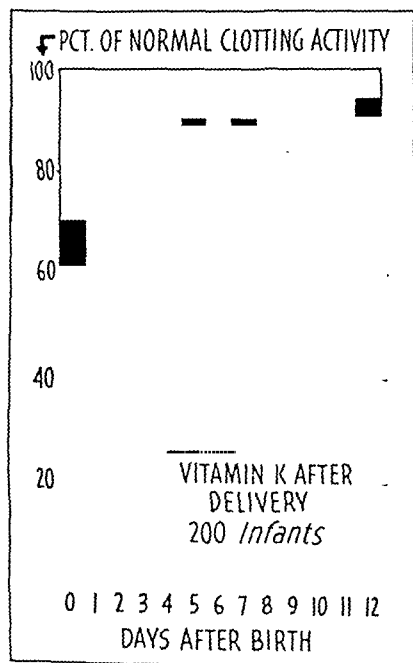


Fig. 5.

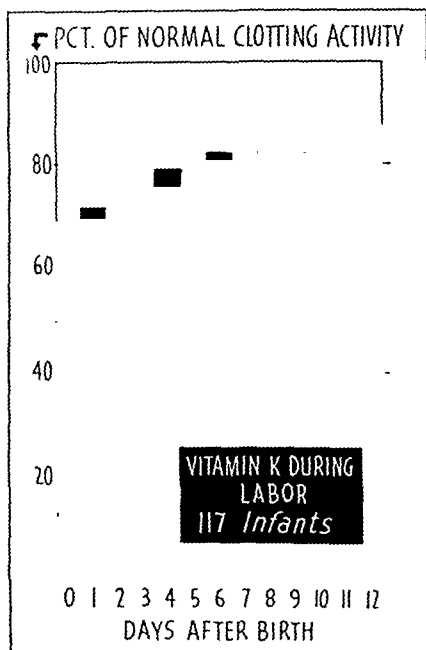


Fig. 6.

Fig. 5.—The administration of vitamin K six and thirty hours after delivery.

Fig. 6.—The administration of vitamin K during labor.

TABLE I. INFANTS WITH CLOTTING ACTIVITY BELOW 30 PER CENT

DAYS AFTER BIRTH	NO VITAMIN K %	VITAMIN K DURING LABOR %	VITAMIN K AFTER DELIVERY %
0	1.1	None	1.5
1	11.5	0.8	4.0
2	19.2	1.7	1.0
3	19.7	3.4	2.0
4	9.8	None	None
5	6.5	2.5	None
6	2.2	0.8	None
7	1.6	None	None

In Table I are listed the percentage of infants in each of the three groups we have studied whose clotting activity decreased to 30 per cent or less of normal. It will be seen that the vitamin K preparation is remarkably effective from a prophylactic standpoint by either plan of administration. With some adjustment in the dosage and in the time of administration of the preparation, a complete prevention of the decrease may be anticipated. From study of our data we would suggest that administration of 4 mg. of 2 methyl-1, 4 naphthoquinone at an interval greater than two hours before delivery, will prevent a significant decrease in the prothrombin level of the blood in more than 95 per cent of infants during the neonatal period. We would also suggest that all infants whose mothers have not received vitamin K at an interval greater than two hours before delivery should receive 1 mg. of 2 methyl-1, 4 naphthoquinone at intervals of six and twenty-four hours following delivery. We would further suggest that all infants subjected to a prolonged labor or difficult delivery receive a vitamin K preparation during the early days of the neonatal period.

The relationship of vitamin K to hemorrhagic disease of the newborn is now well established. The early reports of Brinkhous, Smith, and Warner,¹⁰ Waddell, Guerry, Bray, and Kelley,²¹ and of Nygaard²² as well as the recent publications by Quick and Grossman,²³ and Poncher and Kato²⁴ leave little doubt that hemorrhagic disease of the newborn is a hypoprothrombinemia and that vitamin K is a specific therapeutic agent.

During the period of our study we have encountered no typical case of hemorrhagic disease of the newborn. There have, however, been 7 infants in whom various hemorrhagic tendencies have become manifested. Without exception, these infants have shown a level of clotting activity below 10 per cent of normal. The hemorrhagic manifestations have included bleeding from the cord stump, vomiting of blood-streaked mucus, and the passage of bloody mucus through the rectum. In two instances convulsive movements were also present. In no infant have similar hemorrhagic tendencies developed in the absence of a low clotting activity of the blood. All of this group responded to the administration of 2 methyl-1, 4 naphthoquinone by a prompt increase in the clotting activity and a cessation of the hemorrhagic tendencies. Fig. 8 illustrates the typical curve of such an infant. This infant (XC-39002) vomited a blood-tinged mucus on the third and fourth days following delivery. One milligram of 2 methyl-1, 4 naphthoquinone was given orally on the

warrant conclusions in this connection. It is quite obvious, however, that vitamin K administered during labor, without previous medication during the prenatal period, is effective in preventing a drop in prothrombin levels during the neonatal period.

DISCUSSION

Our investigation covers the period from September 1, 1939, to August 5, 1940. During this period repeated observations have been made on 506 infants. There were, in addition, 15 stillborn infants and 9 infants who died during the neonatal period. This represents a gross fetal mortality of 4.5 per cent. Of the 9 infants who died during the neonatal period, 2 received vitamin K subsequent to delivery, 4 were born of mothers who received vitamin K during labor, and 3 were in the control group. In 2 of these 9 infants a clinical diagnosis of cerebral hemorrhage was confirmed at necropsy. The mothers of each of these infants had received vitamin K during labor. In the first case (XC-39592) a hydrocephalic infant with a lumbar spina bifida was delivered by low forceps application and extraction. Death occurred forty-two hours after birth, following frequent attacks of cyanosis, impaired respiratory activity, and convulsive movements. Necropsy showed a fracture of the frontal bone and extensive intracranial hemorrhage. The second infant (XC-40921) was delivered naturally following an episiotomy after a forty-hour labor. Respirations were spontaneous and the infant appeared in good condition. A cyanotic attack with difficult respiration occurred twenty-two hours after delivery, and the infant died at thirty-nine hours. A prothrombin determination following the initial evidence of cerebral irritation was 50 per cent of normal. Two milligrams of the vitamin K preparation were given by gavage nine hours before death. Necropsy showed an intracranial hemorrhage as the cause of death. In neither of these infants are we justified in assuming that a low prothrombin level in the blood was a factor in the intracranial hemorrhage. In the first case there was obvious trauma, and in the second infant the clotting activity was not significantly impaired.

Details of the case histories of the two infants have been cited to show that one is not justified in expecting miracles from the use of vitamin K. It is well recognized that the production of a normal clot is only one of the factors in the control of hemorrhage. The permeability and fragility of the capillaries must also play an important role. It seems a fair assumption that trauma will continue to be the predominant cause of intracranial hemorrhage in the newborn. It is, however, a logical assumption to add the statement that an infant subjected to some degree of injury may fail to develop a significant hemorrhage unless a marked decrease in the prothrombin level of the blood is present. Similarly, a mild hemorrhage may become marked as the physiologic decrease in prothrombin develops forty-eight to seventy-two hours subsequent to delivery. From this standpoint, the administration of a vitamin K preparation during the early neonatal period or, perhaps, preferably during labor, should afford some increased protection to the infant.

2. A spontaneous return to a normal level occurs during the first week of life.

3. A wide variation is noted in individual infants in the depth of this decrease and in the rapidity of the return to normal levels.

4. This decrease in clotting activity can be prevented by the administration of a vitamin K preparation to the infants during the early hours of the neonatal period or to the mother during the course of labor.

5. A potential relationship exists between the level of prothrombin activity in the blood and the severity of intracranial hemorrhage.

6. There is a direct correlation between spontaneous hemorrhagic tendencies in the newborn and a low prothrombin activity in the blood.

7. 2 methyl-1, 4 naphthoquinone exhibits an active vitamin K effect.

The vitamin K preparation, 2 methyl-1, 4 naphthoquinone, has been generously furnished by E. R. Squibb & Sons.

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fourth day when the clotting activity was 10 per cent of normal. It had risen to 38 per cent in four hours. A second 1 mg. was given on the fifth day. A reading later on the same day was 84 per cent, and the clotting activity remained within normal limits. There was no further evidence of bleeding.

Such a group of infants offers confirmatory evidence for the statement that hemorrhagic disease is due to a prothrombin deficiency. It is true, however, that infants may show a similar prolonged low level of clotting activity without any evidence of hemorrhage. Such curves were shown earlier in the discussion. Perhaps infants in this group should be looked upon as subclinical cases of hemorrhagic disease. Perhaps there is some other factor necessary to precipitate the hemorrhage.

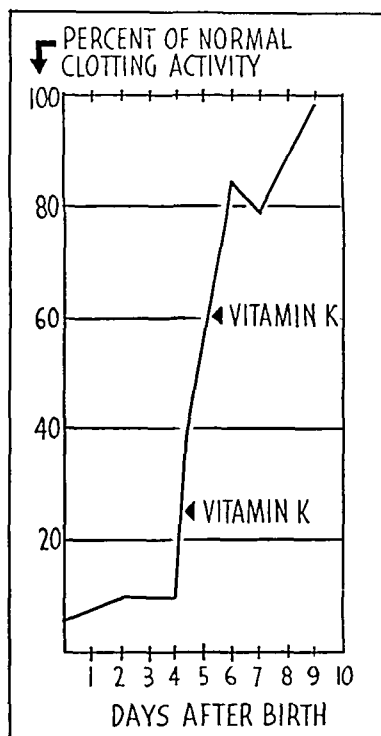


Fig. 8.—The therapeutic effect of vitamin K in hypoprothrombinemia.

SUMMARY

A study of the clinical records combined with laboratory data concerning the clotting activity of the blood of 530 newborn infants confirms the previously reported observation that there is a physiologic decrease in prothrombin activity during the early days of the neonatal period.

The prevention of this decrease by the administration of a vitamin K substance has been investigated.

A simple clinically applicable test for the rapid assay of the clotting activity of the blood has been presented.

CONCLUSIONS

1. Normal infants show a physiologic decrease in prothrombin activity in the blood which reaches a maximum during the third day of life.

DURATION OF LABOR

(Variation)

	<i>Primiparas</i>	<i>Multiparas</i>
1st stage	2½ to 57 hours	1 to 31 hours
2nd stage	5 min. to 7¼ hours	5 min. to 2 hours

(Average)

1st stage	12.6 hours	6.3 hours
2nd stage	1.2 hours	35.1 min.

13 primiparas had 2nd stage over 100 minutes.

1 multipara had 2nd stage over 100 minutes.

FETAL ATTITUDE

Ninety-six of the breech presentations were frank breech, 25 were single footlings, and 13 were double footlings. Sixteen of the single and 4 of the double footlings occurred in premature deliveries.

Duration of Labor in Primipara.—The first stage averaged twelve and six-tenths hours, varying from two and one-half hours to fifty-seven hours. The second stage averaged seventy-one minutes, varying from five minutes to seven hours and seven-tenths minutes. There were 13 patients who had a second stage of over two hours' duration.

Duration of Labor in Multipara.—The first stage averaged six and three-tenths hours, varying from one hour to thirty-one hours. The second stage averaged thirty-five minutes, varying from five minutes to two hours. Only one multipara had a second stage over one hour and forty minutes.

TYPE OF DELIVERY

<i>Manual Aid</i>	<i>Extraction</i>	<i>Section</i>
109	13	4
5 decomposed (1 forcep)	2 forceps	
7 forceps		

The type of delivery is divided into three groups: manual aid, the procedure to be described, extraction, and cesarean section. One hundred nine patients were delivered with manual aid. In 5 of these, the breech was decomposed and then the patient delivered with manual aid. Forceps were applied to the aftercoming head in 7 patients.

Extraction was the treatment in 13 patients. In 3 instances the patient failed to make progress in the second stage and extraction was the procedure then indicated. In 2 of these patients, forceps were applied to the aftercoming head. Two patients had late toxemia of pregnancy, and it was deemed best to terminate the delivery when the cervix was dilated. Two patients, both of whom were multiparas with placenta previa, one with a dead baby, were delivered through the placenta. Six premature twin babies were footling presentations, 2 being the first baby and 4 being the second baby of twins.

Cesarean section was done on 4 patients. Two patients had section for placenta previa, and the breech presentation was incidental. Two patients, both elderly primiparas, were delivered by elective section because they had large babies and it was thought that delivery from below was questionable.

Prolapse of the cord did not occur in the entire series.

FETAL MORTALITY

126 deliveries

15 babies died	Rate 11.9%
5 multiparas	Rate 9.4%
10 primiparas	Rate 13.7%

BREECH DELIVERY*

ELMER M. HANSEN, M.D., LINCOLN, NEB.

THE subject of breech presentation has been discussed in the literature frequently during the past decade. Articles have appeared upholding both the conservative and active management of this presentation, but to date there has been no significant change in the fetal mortality. One is impressed with the fact that the results depend to a great extent upon the ability of the operators to perfect their particular method of treatment.

Most of the communications on this subject have come from large obstetric centers representing, to a great extent, clinic material. The material used as a basis for the presentation of this communication represents the cases of breech deliveries occurring in the associated practice of Dr. Harold S. Morgan and myself over a period of twelve years. It is not a large series of cases, but it represents, we believe, an experience which is comparable to that of the average obstetrician in private practice, and for this reason, we are presenting this series of cases.

During the past twelve years, 1,882 patients were delivered. One hundred and twenty-six babies were presented by the breech, the incidence being 6.7 per cent. This is higher than that usually reported. The incidence of breech presentation during the past twelve years at the Lincoln General Hospital in which 90 per cent of our patients were delivered was 4.2 per cent. Our increased incidence is explained by the fact that a large number of complicated deliveries are referred to us by general practitioners doing obstetrics. The parents of these babies are all white, coming from all social levels, chiefly middle-class American, the foreign element being negligible. The 126 babies were delivered of 120 mothers; four mothers had twin pregnancies in which both babies were presented as a breech, and 2 mothers had breech presentations in two succeeding pregnancies. There were 73 primiparas and 53 multiparas.

SOURCE OF CASES

<i>Hospital</i>	<i>Deliveries</i>	<i>Breech</i>
Lincoln General	1,719	114
Bryan Memorial	118	9
St. Elizabeth	45	3
Total	1,882	126

Incidence	6.7%	No. of mothers	120
	Primiparas	73	
	Multiparas	53	

*Presented before the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

we have delivered 17 sets of twins, or 34 babies. Sixteen babies were breech presentations; seven of the 16 died, all of prematurity. Eighteen babies were cephalic; two of these died of prematurity.

MATERNAL MORTALITY

None

MATERNAL MORBIDITY

*Twelve Cases**Incidence 9.52%*

CASES	CAUSE	METHOD OF DELIVERY	MATERNAL COMPLICATIONS	DURATION	SEVERITY
1	Phlebitis	Section		6 weeks	Severe
1	Pyelitis	Manual aid	Previous cystitis	4 days	Mild
1	Otitis media	Manual aid		4 days	Mild
1	Cystitis	Section	Placenta previa	2 days	Mild
1	Parametritis	Extraction		5 days	Mild
1	Unknown	Manual aid		2 days	Mild
1	Unknown	Bag induction	Toxemia	2 days	Mild
		Manual aid			
1	Unknown	Section	Placenta previa	3 days	Mild
1	Unknown	Manual aid		2 days	Mild
1	Unknown	Manual aid		2 days	Mild
1	Unknown	Section		3 days	Mild
1	Unknown	Manual aid		2 days	Mild

There was no maternal mortality. There were 12 mothers who had a temperature of 100° F. on two succeeding days, excluding the first twenty-four hours post partum. There were 122 confinements, which gives an incidence of 9.8 per cent. Causes of morbidity could not be determined in 7 patients. These were all mild and lasted only two to three days. In 5 patients the cause was known. One patient had phlebitis of the left lower extremity. She had had an elective section. She was in the hospital six weeks and recovered. One patient, with a previous history of pyelitis had a flare-up lasting four days. One patient had acute otitis media lasting four days. One patient with cystitis of two days' duration was delivered by section because of placenta previa, and one patient with a parametritis (tender uterus) had mild symptoms for five days. All 4 patients delivered by section were morbid, but the morbidities were mild, with the exception of the case of phlebitis.

DISCUSSION

The diagnosis of breech presentation was made prenatally in practically every patient coming for prenatal care. Routinely, we carefully check our measurements and estimate the size of the baby. If there is a question of fetopelvic relationship, we use the x-ray as an aid to our decision. External version was not attempted in any patient.

Our method of treatment is conservative. By conservative treatment, we mean giving supportive treatment to the mother with no interference unless labor is obstructed, progress ceases, or complications arise endangering the life of mother, baby, or both.

We were trained in the watchful expectancy method, and from experience we are convinced that meddlesome interference is a definite factor in the difficulties encountered in obstetrics. I am sure that if we all agree that conservatism is good procedure in cephalic presentations it should be rational in the breech.

From personal observation and experience, we have formulated the following points to guide us in breech delivery:

1. Dilatation of the cervix does not become complete in many cases until the buttocks are presenting deeply at the introitus.

<i>Period of Gestation</i>	<i>Abnormality</i>	<i>Weight</i>
Term	None	8 lb. 4 oz.
Term	Spina bifida, hydrocephalus	7 lb. 14 oz.
34 weeks	Anencephalia	5 lb. 4 oz.
27 weeks	Premature	1 lb. 14 oz.
27 weeks	Premature	2 lb. 10 oz.
26 weeks	Premature	2 lb. 12 oz.
25 weeks	Premature (toxemia)	2 lb. 5 oz.
24 weeks	Premature (second of twins)	1 lb. 7 oz.
28 weeks	Premature Twins	1 lb. 9 oz.
28 weeks	Premature Twins	1 lb. 10 oz.
33 weeks	Premature (No fetal heart tones)	4 lb. 15 oz.
	Placenta previa	
28 weeks	Premature Twins	2 lb.
28 weeks	Premature Twins	1 lb. 10 oz.
27 weeks	Premature Twins	1 lb. 7 oz.
27 weeks	Premature Twins	1 lb. 8 oz.

Summary of Fetal Mortality

Term:

1 Intracranial hemorrhage

2 Monsters

Premature:

1 33-week placenta previa. Stillborn.

No fetal heart tones on admission.

11 period of gestation, 24 to 28 weeks.

Weight varying from 1 lb. 7 oz. to 2 lb. 12 oz.

Corrected mortality 0.8 per cent

Fifteen babies were stillborn or died neonatally. This gives a gross mortality of 11.9 per cent. Five deaths occurred in multiparas (9.4 per cent), and 10 in primiparas (13.7 per cent). Eleven babies were definitely premature, the period of gestation ranging from twenty-four to twenty-eight weeks, and the weights varying from 1 pound 7 ounces to 2 pounds 12 ounces. Several were one or both of twins. One baby was of thirty-three weeks' gestation, and the mother, a multipara, had central placenta previa and no fetal heart tones on admission. Three patients were at term. One normal baby, weighing 8 pounds, 4 ounces, was delivered by manual aid after a second stage of five hours. The baby lived eight hours and fifteen minutes, and died suddenly. Post-mortem examination revealed intracranial hemorrhage and a large cephalohematoma. One baby was hydrocephalic with a large spina bifida; it did not cry and lived only a few minutes. The third full-term baby was an anencephalic monster. Excluding the premature and abnormal babies, there remains only one fetal death or a corrected incidence of 0.8 per cent.

FETAL MORBIDITY

One baby who presented a frank breech was delivered by extraction after spontaneous delivery of the umbilicus because both arms were extended. The baby required resuscitation. Inspection revealed marked asymmetry of the face, with a depression of the vault into which the forearms fitted. This baby had bilateral Erb's palsy when delivered. The right arm recovered in seven days and the left arm in three weeks. The left clavicle was fractured during delivery. One other baby had a fractured clavicle. Three babies developed cephalohematomas, and several babies developed hematomas of the sternocleidomastoid muscle. They all developed after the patient left the hospital. No known serious sequelae followed.

TWINS

Twin incidence was interesting. In our series of breech presentation, 8 babies were one of a set of twins; one of these died of prematurity. Eight babies represented both babies in 4 sets of twins. Six of these babies died. In the twelve years

DR. IRVING F. STEIN, Chicago, Ill.—A complete breech is one with the fetus in the attitude of complete flexion, and the incomplete breech is one of deflexion attitude. I do not believe that this has been emphasized in obstetric literature. In incomplete breech one frequently observes the fetus in a military attitude with the head erect or sometimes turned to the side or even tilted back, like an inverse brow presentation. A greater amount of mobility of the fetus is evident with breech than with cephalic presentation. Even with complete breech you may occasionally find a displaced arm and the head a little deflexed; this can be discovered only by x-ray examination. The practical application of this procedure enables you to be forewarned and prepare for manual aid or extraction.

The points I wish to emphasize are first, that incomplete breech is an example of a deflexion attitude; second, in cases of breech particularly, you can obtain much practical information by taking roentgenograms before delivery which would otherwise be missed by ordinary methods of examination.

DR. RUDOLPH W. HOLMES, University, Va.—Some 75 years ago Carl Braun reported in his textbook on 67 cases of face presentation which were seen in his clinic. He stated as a result of that great experience that a face presentation in a primiparous labor was *prima facie* evidence of a pelvic deformity.

In our more mature knowledge of pelvic abnormalities we now know that pure pelvic asymmetry is as potent a cause as is definite contraction. We may further state that the flat pelvis and the obliquely contracted types are more prone to produce malpositions and presentations than the symmetrical generally contracted pelvis.

Not only is a face presentation produced by these factors, but we may broaden that statement to the rule that all deviations of presentation are sequential to aberrant contours of the pelvic brim. In my own experience a breech delivery with a *normal* pelvis is as physiologic and as safe as the normal vertex positions. On the other hand, when there is any disproportion, the breech delivery is fraught with the greatest difficulty and danger.

I still believe that it is the exceptional case of breech which demands a cesarean section. Contributing factors which are of etiologic importance may more often indicate cesarean operation than similar conditions in a vertex position.

DR. R. S. SIDDALL, Detroit, Mich.—I want to make a few remarks on the basis of a recent monograph which Dr. Seeley and I have published. We found in going over a considerable number of papers in the literature that there were several series of 100 or 150 cases in which the results were comparable with those of Dr. Hansen. We did not find, however, any series of 200 or over which did not have a very considerable increase of fetal, not maternal, deaths associated with breech.

In our series from the Herman Kiefer and Harper Hospitals in Detroit it was noticeable, however, that we would often have 125 or 150 cases in a series with only one or two deaths. Although one may have a relatively small series with good results, one eventually encounters difficulty.

External version is associated with very little danger. It is very reasonable to employ an easy and safe procedure to convert a dangerous presentation associated with from 5 to 20 per cent mortality into one with only 1 or 2 per cent mortality.

We found that there were three things which contributed very largely to excessive fetal mortality in breech: (1) The mortality increases with babies weighing from 8 pounds to 9 pounds and over until it reaches 20 to 25 per cent. (2) Elderly primiparas have a "lamentable" fetal mortality, as someone expressed it in the literature. It may be around 25 to 30 per cent. (3) Contracted pelvis also has a high mortality, even in the minor grades of pelvic contraction.

DR. A. F. LASH, Chicago, Ill.—As a result of an extensive experience at the Cook County Hospital in Chicago, where we deliver over 5,000 babies a year, there are certain points which are crystallized in our minds regarding breech delivery.

2. Attempted delivery before complete dilatation is almost certain to result in extension of arms and head with difficulty in delivery.

3. It is natural for the force to be applied from above. Application of force from below by traction is not the normal force. Extension of the arms, nuchal arms, and extended head are the result of force applied from below rather than from above.

4. Manipulation from below, especially if the patient is not deeply anesthetized, will reflexly stimulate tetanic contraction of the cervix or lower uterine segment; this contraction imprisons the shoulders and cephalic pole in the uterus and delays delivery; it also necessitates increased force which traumatizes both mother and baby.

5. Gentleness in all maneuvers is of the greatest importance.

CONCLUSION

We have reported a series of 126 breech deliveries occurring during twelve years of private practice, with a corrected fetal mortality of 0.8 per cent.

Conservative treatment in our hands has produced satisfactory results. Teamwork is an important feature of our treatment, and we believe it has had a definite influence on our results.

Prematurity, especially prematurity in twin pregnancy, accounted for 80 per cent of our fetal deaths. Efforts toward preventing premature labor in twin pregnancies should lower the gross fetal mortality of breech presentation.

This communication deals with private practice only. The reporting of many similar analyses and comparing them with reports from the clinic groups, we believe, would be worth while.

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DISCUSSION

DR. DAVID L. SMITH, Indianapolis, Ind.—The staff of the University Hospital at Indianapolis is essentially a closed one, made up of members of the teaching staff. There are two and one-half ward patients to one private patient. There were 190 breech presentations in 1,264 deliveries. Of the 31 stillbirths 4 were monsters, 6 were macerated fetuses and 6 were premature. There were 11 deaths attributable to the breech presentation, so the corrected mortality was 5.78 per cent, which is a great deal higher than Dr. Hansen's. I have no way of accounting for that difference, except possibly on the basis that our service is somewhat of an emergency service, being a state hospital which admits patients from all over this portion of the state who have received no prenatal care and who sometimes are desperately ill.

Review of the charts sometimes leads to conclusions as to what not to do. Two of the deaths occurred in labors which had been induced, both of which were definitely past term by history. In both the babies weighed a little over 5 pounds. One of the cardinal principles in breech management is to avoid induction of labor.

We believe in external version as long as it is done with gentleness and without anesthesia. We personally have been successful in external version in about 60 per cent of the trials. Cesarean section should probably play a greater part in the management of breech delivery.

We use intermittent nitrous oxide and oxygen anesthesia, and then change to drop ether at the time the umbilicus is born. We are using forceps on the after-coming head more and more because we believe it is less traumatic to the baby than any other method of delivery.

mature separation of the placenta and another with rupture of the membranes, and prolapse of the cord. Before the situation could be analyzed, the baby died. Also, we have had unusually good results in the series without doing external version.

In answer to Dr. Stein: We do not maintain forcible but a steady fundal pressure so as to control, if possible, the flexion of the aftercoming head.

Four patients had cesarean section, two with placenta previa and the breech presentation was incidental. The other two were elderly primiparas. One was 43 years old, having her first baby, which weighed over 9 pounds. The other primipara was 38 years old and delivered a baby which weighed 9 pounds, 15½ ounces. I believe that these are real indications. As it is, our incidence of cesarean section is very low.

I would like to say a little something about the general practitioner and his treatment of breech presentation. A few years ago we investigated the fetal mortality in our hospitals, and there was one hospital in our state that had a fetal mortality rate of 33 per cent in breech presentation over a period of three years. At the Lincoln General Hospital where we have done most of our work, we have a set of rules regarding our obstetric department. No man, and it makes no difference whether he is a member of the obstetric staff or a visiting man who brings in a patient for delivery, can do an operative delivery and that includes breech extraction, without consultation. It is his privilege to call in a member of the obstetric department for consultation, which service must be rendered free of charge. Under the influence of that rule our fetal mortality was lowered to one-third of what it had been for the previous five years. It has now been in effect for approximately five years. The general practitioner usually interferes. It would be preferable for him to be more conservative.

ARE THE ANTERIOR PITUITARY-LIKE SUBSTANCES GONADOTROPIC?*

A CLINICAL EVALUATION IN THE WOMAN

WILLIS E. BROWN, M.D., JAMES T. BRADBURY, D.Sc.,
ANN ARBOR, MICH., AND IDA METZGER, M.D., YPSILANTI, MICH.

(From the Department of Obstetrics and Gynecology, University Hospital and Ypsilanti State Hospital)

THE anterior pituitary-like substance from human pregnancy urine has been available for clinical use during the past decade. However, the medical literature is not unanimous in its opinion regarding the physiologic effects of this material. The well-known gonadotropic response obtained in the mouse and rabbit is not found consistently throughout laboratory animals, nor has it been duplicated in the human female in any manner that will stand critical evaluation.

The clinical reports in the literature are based on patients who were treated for some menstrual abnormality of uncertain etiology and unpredictable course. On the basis of such observations, many authors enthusiastically recommend its use, but here and there are reports of dissenting opinion.

Geist¹ described atretic follicles with hemorrhage in women treated with antuitrin-S. Rock² described probable degeneration of follicles in women following its use. Hamblen³ called attention to premature and increased involutional changes

*Presented before the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

First, breech presentations can deliver spontaneously as well as cephalic. This point requires special emphasis because when we get into discussions with the doctors in the surrounding rural communities, they say, "How can we deliver these babies without getting a 90 per cent fetal mortality?" Too often the conception is that as soon as the presenting part is visible, immediate extraction is started and it is associated with complications.

Second, with regards to analgesia, we feel that we want the cooperation of the patient throughout labor. We never use the barbiturates during the first stage. If the patient is in strong labor and requires some rest, we feel morphine and scopolamine fulfill that requirement. Pudendal block and local infiltration of the perineum and pelvic floor will allow complete cooperation of the patient which helps in the delivery of the baby.

We do not feel that eight minutes between the appearance of the cord and the delivery of the head is so important. We have found that as much as fifteen minutes can be taken in the delivery of the head as long as air reaches the mouth by retracting the perineum. It is at this point that the greatest harm is done to the baby by undue traction. When we feel that the head seems to meet with a good bit of obstruction, instead of continuing the extraction we usually release our pull on the baby's head; we push the baby up, which allows increased flexion of the head, bringing the head down in the transverse diameter, thereby facilitating delivery of the head. With this in mind, I think we avoid damage to the baby and lower our fetal mortality.

DR. FREDERICK H. FALLS, Chicago, Ill.—Breech is more common in the arcuate type of bicornate uterus, which is seen relatively frequently. When breech is present in such a uterus, it is very difficult or impossible to do external version, and I think it is often dangerous even to try. We feel that not infrequently a combination of arcuate type of bicornate uterus and breech is a relatively strong indication for cesarean section. Since adopting this policy, we have had very much better results in this type of case.

In placenta previa we frequently have an associated breech presentation, because under this circumstance the breech will fit the lower uterine segment better than the head. The combination of breech and placenta previa is also a relative indication for cesarean section.

The importance of the fact that the premature baby frequently presents by the breech cannot be overemphasized. The more premature the baby is, the more reason there is for thoroughly dilating the birth canal. In these cases we thoroughly dilate the birth canal and do an episiotomy to avoid cerebral damage to the premature baby during delivery.

DR. J. C. LITZENBERG, Minneapolis, Minn.—If you will change the term "external version" to "attempted external version" you will avoid a lot of arguments. I have always taught that external version should be attempted but I have never persisted in it if it offers any difficulties whatsoever. There are certain conditions in which it should never be attempted. It is a shame in a case where external version could be done with the greatest of ease not to do it, but it is also a shame, and a greater one, to persist in its use when one has difficulty.

DR. E. M. HANSEN (closing).—Dr. Morgan and myself have always tried to be conservative in our estimation of our ability to do a good job delivering a breech, and I am very frank with you when I say there has been a question in my mind as to just how much luck we have had in our series. As time has gone on each breech presentation has been a very definite challenge to us, and I think in that respect this challenge has had a very definite influence on our work, because we have tried every time to get a live baby.

With regard to external version, not once was it attempted. The reason for this is that in my period of training I saw many external versions attempted and but very few of them successful. On two occasions babies were lost, one with pre-

these patients. In order to determine whether the physiologic activity of antuitrin-S is predominantly follicle-stimulating or luteinizing, some of the patients were treated in each phase of the cycle; namely, after the menstrual period (follicular phase) and just after the midinterval (early corpus luteum phase).

The normal menstrual and endometrial rhythm was not appreciably altered in 7 (58 per cent) of the 12 patients. Fig. 1 abstracts the records of 4 of these subjects. On the basis of endometrial histology it appears that C. R. had an anovulatory cycle just preceding and again during treatment. Antuitrin-S in the dosage given did not cause ovulation or corpus luteum formation in this case, although there was a slight irregularity in the subsequent menstrual rhythm. Another patient, M. W., skipped a menstrual period one month after treatment. This suggestion of an induced amenorrhea is more apparent in the menstrual histories of the patients in Fig. 2. Five (42 per cent) of the 12 patients treated experienced a temporary amenorrhea of from one to five months. Endometrial biopsies taken in the early stages of this amenorrhea are characterized by a resting endometrium, suggesting a suppression of follicular maturation.

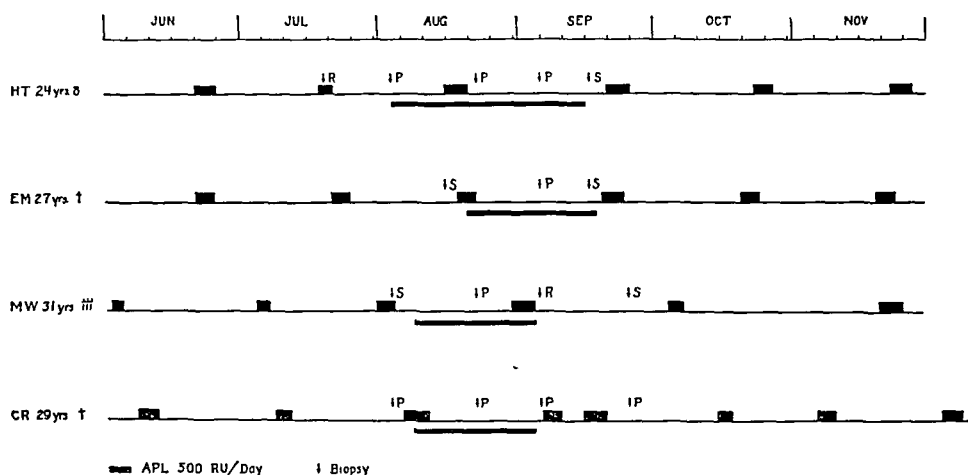


Fig. 1.—Effect of antuitrin-S on women with normal menstrual cycles. Note: C. R. had an anovulatory cycle before and during treatment.

The patients with an unexplained amenorrhea of one or more years' duration were studied in a similar manner. A first-voided morning specimen of urine was concentrated by the alcohol precipitation method of Zondek, as modified by Frank,⁸ and was assayed for pituitary gonadotropic hormone. The test was negative in each instance, indicating the patient had not gone through a premature menopause. This was verified by the subsequent return of menses in 4 of these patients. The dosage of antuitrin-S was the same in this group as in the normal patients, 500 R.U. daily for four weeks. Two controlling biopsies were taken before treatment.

The first 2 patients in Fig. 3 are excellent examples of the unpredictability of the return of menstruation. In each case a normal menstrual period occurred during the two weeks' observation period before treatment was started, even though they had had nineteen months and twelve months of amenorrhea, respectively. Treatment was started on M. B. on the day of the second biopsy and was continued even though menstrual function was re-established. In view of the amenorrhea induced in normal patients, it is interesting that this patient (M. B.) had only 2 menstrual periods,

in ovaries of treated women. Eisenstaedt⁴ and others⁵ have described various apparently noxious changes in the testis resulting from the use of P.U. extract in treatment of cryptorchidism.

The present study was arranged to determine by clinical experimentation whether the anterior pituitary-like extracts of pregnancy urine have any demonstrable effect on the human ovary. The physiologists and the pharmacologists select normal animals under standard experimental conditions for testing drugs. This investigation was carried out along parallel lines by studying first the effect of antuitrin-S on the normal ovary, then on the abnormal.

In hoping to approximate ideal experimental conditions for clinical research, we considered the following factors as basic requirements for any satisfactory interpretation of results. (1) The group of patients should be fairly large and live in a uniform environment. (2) They should be of good health, similar age and past reproductive history. (3) They should have an accurate menstrual record for twelve months prior to study, and during an observation period of at least six months following treatment. (4) Since it is impossible to make observations of the ovary itself, endometrial biopsies should be taken at frequent intervals, as they offer conclusive objective information regarding ovarian activity. While Bartelmez⁶ and a few others have found several stages of endometrial development in a single uterine specimen taken during menstruation, it is well established⁷ that the rhythm of the endometrial histology parallels the ovarian cycle and indicates the functional state of the ovary.

To fulfill these experimental requirements most satisfactorily, the patients should be institutionalized during the course of the investigation; those of the Ypsilanti State Hospital were made available to us for study. Patients with a normal menstrual rhythm during the previous year of hospitalization were examined, and 12 were selected who had no palpable pelvic abnormality, who were fairly stationary in regard to their psychoses, and who met all the above requirements. Most of these patients were multiparas; this supports our findings of an essentially normal generative tract. A second group of patients with a hospital record of at least twelve months' amenorrhea were also examined, and 7 were selected for study. Since no apparent cause for the amenorrhea could be found on clinical examination of these patients, amenorrhea was thought to be due to the psychosis.

Endometrial biopsies were taken with the Novak suction curette at frequent intervals before, during, and after treatment; a total of 143 endometrial samples were obtained from 19 patients. Menstrual records were kept throughout the period of treatment and for several months after the cessation of treatment. One cubic centimeter (500 R.U.) of antuitrin-S* was administered daily for four or six weeks. Even though this is a larger dose than is used clinically, except in unusual cases, no untoward local or systemic reactions were noted in

*Antuitrin-S was freshly manufactured material furnished through the courtesy of Parke, Davis & Co.

The records of these patients are charted in Fig. 4; the patients restudied may be identified by their initials and ages in the previous figures. E. C. previously had a three months' amenorrhea following treatment but in this study she skipped March; her April bleeding was anovulatory. E. M. had previously shown no effect but in this series she developed an anovulatory period in March, and in April no endometrium could be obtained; she skipped her May period. C. R. had an anovulatory period in both the first and present series, and as indicated, this was followed by an amenorrhea of five months. Again the deviation from the normal following antuitrin-S therapy is a tendency toward an induced anovulatory bleeding or amenorrhea. The patients with an unexplained amenorrhea were not benefited by this treatment.*

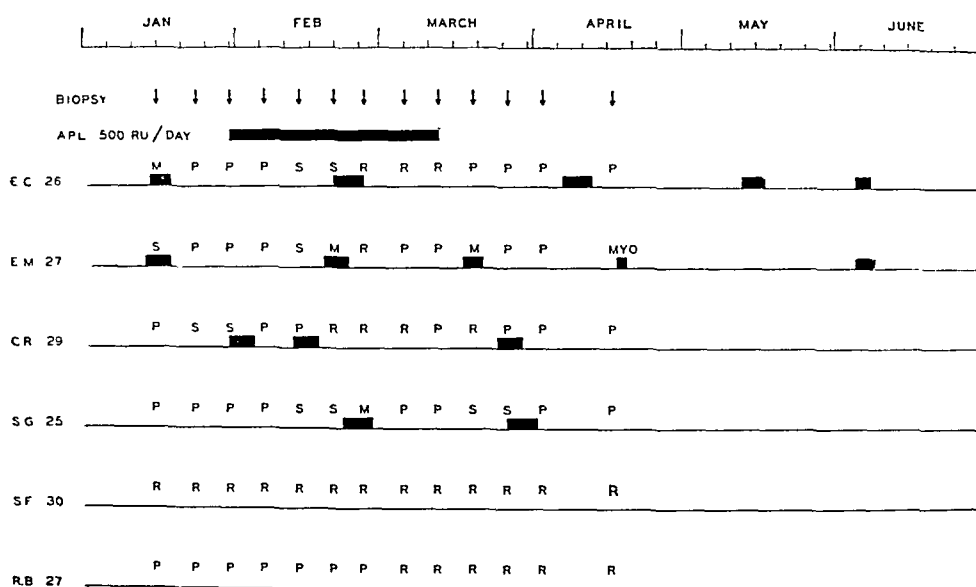


Fig. 4.—Late effect of antuitrin-S on endometrium of menstruating and amenorrheic patients (see also footnote).

As the period of treatment entered the fifth week, it became increasingly difficult to obtain any endometrium from the patients, and frequently only portions of the basalis or myometrium were found. The endometrium showed a progressive atrophy that approached the menopausal state. The atrophy is evident in the biopsies shown in Fig. 5. Antuitrin-S apparently suppressed ovarian function to such an extent that the secretion of estrin was reduced and the endometrium atrophied. This suppression of follicular maturation in the human ovary is similar to the findings of Engle⁹ and Smith,¹⁰ who report a definite follicular atresia and suppression of estrogenic hormone in the monkey by anterior pituitary-like substances. Their work is of interest since the monkey has a menstrual cycle very comparable to that of woman.

Since a daily dose of 500 R.U. did not produce any significant alteration of the menstrual cycle in the majority of patients, a dose of at least twice this amount would be necessary to induce consistently an amenorrhea by the suppression of ovarian activity. The lack of any stimulative effect at the dosage used in this study makes it seem probable that the published reports of correction of menstrual abnormalities during treatment with doses of 100 to 500 R.U. per week are coincidental rather than treatment effects.

In view of this demonstrated suppression of ovarian activity, there would be no indication for the use of the anterior pituitary-like sub-

*S. G. was having a remission from her psychosis during March and April and was being paroled for short visits at home. The occurrence of these 2 menstrual periods was undoubtedly more closely linked with her improved mental state than with coincident therapy.

while the patient who was not treated (A. B.) continued to have regular menstrual cycles. The other patients shown in Fig. 3 did not menstruate as a result of treatment, and the endometrial biopsies give no indication of any increased ovarian activity. An attempt was made to get twenty-four-hour urine specimens for estrogen assay before and during treatment. Due to the inability of the patients to cooperate in this portion of the study, the results can be considered as suggestive only. The findings that were obtained failed to show any change in estrogen excretion during treatment.

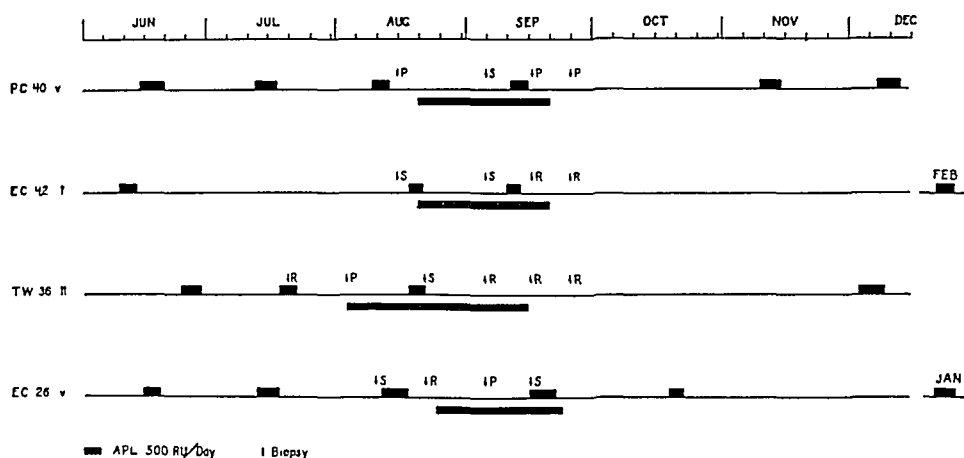


Fig. 2.—Temporary amenorrhea induced in 5 of 12 (42 per cent) women with regular cycles by antuitrin-S.

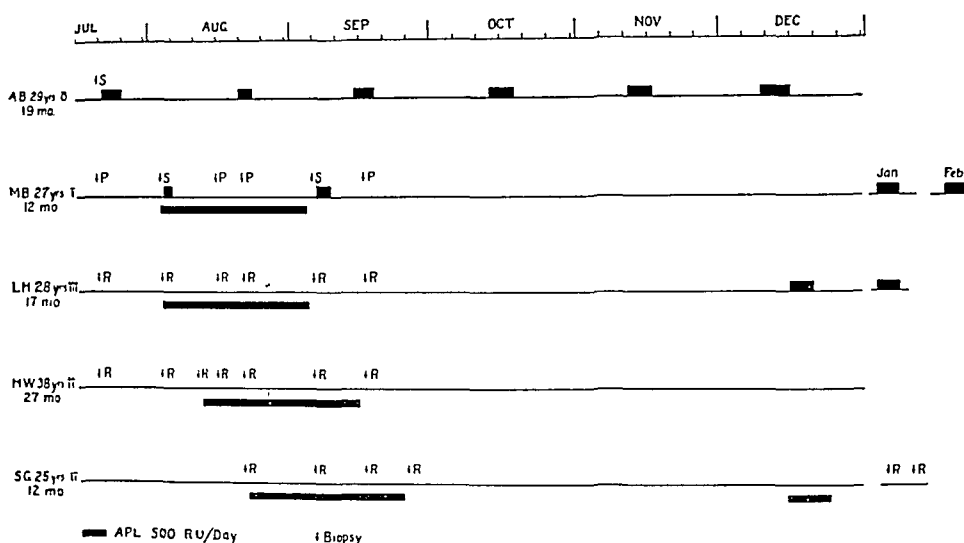


Fig. 3.—Patients with unexplained amenorrhea treated with antuitrin-S. Note: Two patients, A. S. and M. B., resumed menses during period of observation, and M. B. had a three months' amenorrhea following antuitrin-S treatment.

Having obtained these results, we instituted a second period of treatment on a small group of patients to see whether the findings of the original series could be duplicated and to obtain more detailed information on the condition of the endometrium during and following treatment by a study of a more complete series of biopsies. Antuitrin-S (500 R.U. daily) was given to 3 normal and 3 amenorrheic patients for six weeks, and biopsies were taken once a week for twelve weeks.

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DISCUSSION

DR. JAMES T. BRADBURY, ANN ARBOR, MICH.—Dr. Brown has presented evidence that the human ovary is suppressed rather than stimulated by the anterior pituitary-like substance from human pregnancy urine. His evidence for follicular suppression is based on the definite involution of the endometrium which was observed during treatment. This is in accord with the observations of Engle on the monkey, where it was shown that this A.P.L. substance caused a follicular atresia and a diminished production of estrogen. There was no evidence of any luteinizing activity in this series of patients since, judging from the endometrial histology, at least five of them failed to form an active corpus luteum during the period of treatment and the life of the corpus luteum was not prolonged in any instance. Having failed to demonstrate either a follicle-stimulating or a luteinizing effect, both of which have been claimed for A.P.L., it may be well to evaluate the evidence upon which these effects have been established.

The present concept of the gonadotropic function of A.P.L. is largely based on the changes in the ovary of an immature rat or mouse that has been treated for ninety-six hours and then autopsied. At that moment the picture is one of ovarian stimulation and precocious maturity. However, when these animals are allowed to survive, the majority of them have been found to be sterile. When newborn female rats and mice are treated, they are all rendered permanently sterile. This induced sterility is not part of the usual concept of a gonad-stimulating substance. The detrimental end results of treatment may change the interpretation of the apparent stimulative effects seen in the Aschheim-Zondek reaction. Even the immediate effects of this anterior pituitary-like extract are not consistent in different animals. The guinea pig ovary does not show any stimulative effect. The field mouse does not respond at any dosage, and the deer mouse responds only when massive doses are given. A more prolonged treatment in guinea pigs, or in newborn rats and mice, leads to definite masculinization and sterility.

In view of these inconsistent responses of the different animals, it appears that the Aschheim-Zondek reaction upon which the usual concept of follicle-stimulating and luteinizing effects is based is an atypical reaction. A broader analysis of the situation indicates that A.P.L. is more frequently a depressor or an inhibitor of ovarian function.

With this experimental background it is obvious that the clinical findings presented by Dr. Brown represent another instance of the inhibiting effect of A.P.L. on the ovary. This substance excreted in the urine of pregnant women is elaborated by the placenta, but its purpose or function is still a matter of conjecture. It certainly plays no part in the physiology of the nonpregnant woman, so that it is not surprising that it has so little demonstrable action on the human ovary.

It is well known, however, that A.P.L. is gonadotropic in the male for it stimulates the testis to produce male hormone and may even accelerate spermatogenesis. This fact does not make a valid argument that it should also stimulate the ovary. The best evidence shows that A.P.L. is most frequently an inhibitor of ovarian function and, for that reason, we have suggested that A.P.L. is gonadotoxic rather than gonadotropic as far as its effect on the human ovary has been demonstrated.

stances in ovarian hypofunction. The apparent success of antuitrin-S in some cases of functional bleeding can be more satisfactorily explained as the result of a suppression of ovarian follicles, so that the endometrium is relieved of a prolonged estrogenic stimulation. A total dose of 8,000 R.U. over a period of two weeks produced a four months' amenorrhea in one of our patients who had been bleeding continuously for eight months.

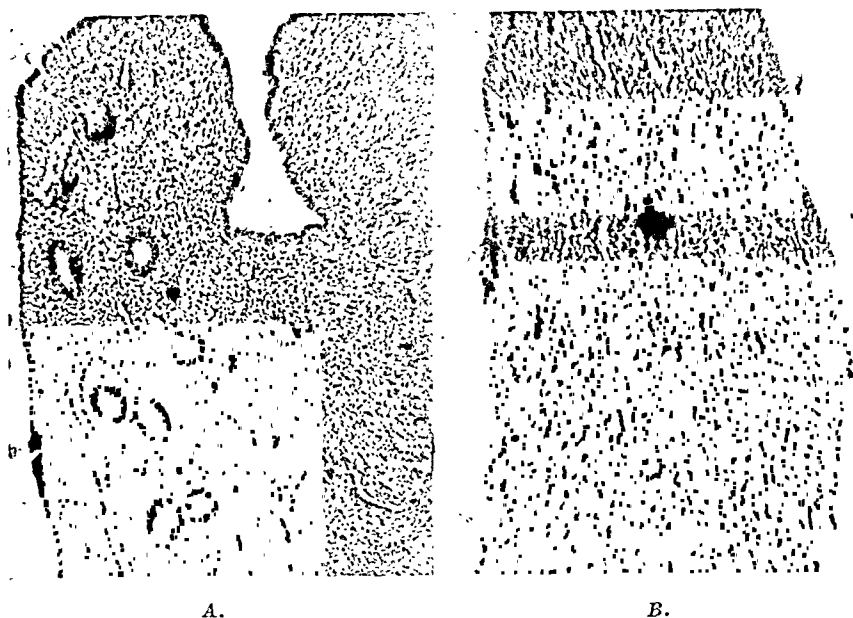


Fig. 5.—Endometrial atrophy produced by antuitrin-S (same magnification). A, 1/30/40 before treatment; B, 3/5/40 two weeks after treatment. Note: See Fig. 4, EM.

SUMMARY

Twelve patients with a normal menstrual rhythm were given 500 R.U. of antuitrin-S daily for four or six weeks. The majority of these patients did not show any significant alteration in rhythm. Five (42 per cent) experienced an amenorrhea of from one to five months following treatment. This induced amenorrhea was accompanied by a progressive atrophy of the endometrium, indicating a suppression of ovarian follicles.

Antuitrin-S failed to establish uterine bleeding in patients with amenorrhea. No evidence of ovulation or luteinization, as demonstrated by a secretory endometrium, was found.

On the basis of this experiment it appears that the anterior pituitary-like substances are not gonadotropic in the human female and in sufficient dosage may even be gonadotoxic.

We wish to express our indebtedness to Parke, Davis & Co. for furnishing the material used in this study and for financial support which made possible the technical assistance of Miss Helen McRae. We also wish to take this opportunity to thank Dr. Yoder and his staff for their cooperation and permission to use their patients; and especially, Marie Dahl, R.N., who gave the treatments and supervised the care of the patients during this study.

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extract, alone and free of other factors, in dystocia during the first stage of labor due to uterine inertia. The largest group of records eliminated were those with obvious or possible doubt as to the existence of actual labor when the substance was given. By accepting only the patients with obliteration of the cervical canal and beginning dilatation of the external os, as well as regular though weak labor pains, it seems probable that false conclusions due to the inclusion of any substantial number of simple inductions of labor or false labors were largely obviated. Reasons are obvious, we believe, for the other restrictions upon acceptance of cases into the studied series.

During the five-year period preceding December 31, 1939, a total of 62 patients were delivered at Herman Kiefer Hospital, whose labors conformed to the criteria given. Thirty-seven were delivered of their first children, and 25 had had one or more previous full-term or premature deliveries. As shown in Table I, occurrence of the different fetal positions approximated the usual distribution.

TABLE I. DISTRIBUTION OF PATIENTS IN REGARD TO FETAL POSITION

POSITION	PRIMIPARAS	MULTIPARAS	TOTAL
O.L.A.	17	16	33
O.R.A.	6	6	12
O.L.P.	2	0	2
O.R.P.	11	3	14
Breech	1	0	1
Total	37	25	62

The substance used was principally the solution of the oxytocic principle of the posterior pituitary lobe (pitocin) in a strength of 10 international units per cubic centimeter. In some instances the extract of the whole lobe in obstetric strength (10 international units per cubic centimeter) was given, and here, as seems to be generally conceded, there was no apparent difference in the oxytocic activity of the two preparations. The substances were given hypodermically in doses twenty to thirty minutes apart, beginning with 1 to 3 minims and increasing a minim with each dose up to a maximum of 5 minims. The course was discontinued at the point where good stimulation of uterine contractions occurred; or where there was little effect, after 5 or 6 doses. The fact that in 19 cases there was strong, and in one of these excessive, stimulation following initial injections of 2 to 3 minims suggests that for safety the first dose should perhaps be no larger than 1 minim. It also should be noted that in a few instances the administration of quinine preceded the pituitary extract, and in 5 instances artificial rupture of the membranes was done in association with the use of pituitary extract. For the sake of completeness, it is perhaps well to add that, in addition to the special measures outlined, these patients also received the usual supportive treatment, including intravenous glucose solution and rest periods induced by morphine or other sedative drugs as indicated. Tables II and III illustrate the stimulating effectiveness of the gland extract.

PITUITARY EXTRACT FOR DYSTOCIA DUE TO UTERINE INERTIA IN THE FIRST STAGE OF LABOR*

R. S. SIDDALL, M.D., AND D. G. HARREL, M.D., DETROIT, MICH.

(From Herman Kiefer Hospital and the Division of Obstetrics and Gynecology, Wayne University)

THE early employment of posterior pituitary extract, in large doses, as an oxytocic resulted in such serious accidents as to bring about condemnation of its use in labor before delivery of the child. Williams, in referring to pituitary extract in uterine inertia, says, "... its administration is reprehensible during the first stage of labor." Titus agrees with this, without qualification, except to include the second stage as well. "However," to quote Faber and Mussey, "it remains a fact that many competent practitioners in rural and outlying communities have continued its use in smaller doses than were used originally, with a fair measure of success, often obviating the necessity for operative termination of labor under conditions decidedly unfavorable." Inquiry will quickly show that such use is not confined to outlying communities but indeed is practiced to an extent in some large clinics here and abroad (DeLee, Gavaudan). In our opinion the fact that large doses are undoubtedly highly dangerous does not necessarily mean that small quantities of the substance should be so harmful as to be totally contraindicated. For some years now at Herman Kiefer Hospital, pituitary extract in small doses has been given in selected cases where stimulation of inefficient labor pains would be of great advantage. The present investigation was undertaken to indicate the results, both as to efficiency and dangers, of such use in prolonged labors due to weak labor pains.

The patients studied were those with prolonged labor (thirty hours or over) in whom pituitary extract was given in the first stage of labor for weak pains, and in whom:

1. There was definite evidence that true labor had begun.
2. Inefficiency of labor pains, or uterine inertia, was apparently the chief or only cause of dystocia.
3. Delivery occurred at term of a single child weighing 2,500 Gm. (5 pounds 8 ounces) or over.
4. The child was alive when pituitary extract was started.
5. There was no fetal anomaly or any complication seriously jeopardizing the fetus, such as prolapsed umbilical cord or toxemia of pregnancy.
6. There was no major interference in labor before pituitary extract was given.

Limitation of cases to those which were in accord with the foregoing criteria appreciably reduced the number available for study. However, this exacting selection seemed necessary in order to assure as nearly as possible a clear-cut consideration of the effects and results of pituitary

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TABLE III. STIMULATING EFFECT ON LABOR PAINS OF INDIVIDUAL SERIES OR COURSES OF PITUITARY EXTRACT INJECTIONS (INITIAL 62 AND REPEAT 22) IN PRIMIPARAS AND MULTIPARAS AND EFFECT ACCORDING TO DILATATION OF THE CERVIX

STIMULATION OF PAINS	PRIMIPARAS				MULTIPARAS				GRAND TOTAL
	CERVIX LESS THAN 3 CM.	CERVIX 3 TO 6 CM.	CERVIX 6 CM. PLUS	TOTAL SERIES OF INJECTIONS	CERVIX LESS THAN 3 CM.	CERVIX 3 TO 6 CM.	CERVIX 6 CM. PLUS	TOTAL COURSES OF INJECTIONS	
Slight or temporary	4	10	8	22	8	11	0	19	41
Moderate	2	0	2	4	2	1	0	3	7
Strong	4	10	4	18	2	7	4	13	31
Strong with artificial rupture of membranes	0	1	1	2	2	0	1	3	5
Total	10	21	15	46	14	19	5	38	84

only cases of true first-stage dystocia were included. At the same time, however, it eliminated a large number with originally poor pains in whom successful use of the substance had resulted in delivery before thirty hours, whereas those with poor results tended to go the time limit and were included in the study. Furthermore, a review of the 20 failures in the series showed that, though stimulation was reported as slight or temporary, there was better progress subsequent to the injections in a substantial number. Indeed, even in these so-called failures, operative intervention before full dilatation of the cervix was required in only 3 instances, i.e., introduction of a hydrostatic bag in 1, and incision of the cervix (Dührssen) in 2. Such interference was not necessary, of course, in the 42 where the extract gave moderate to strong and lasting stimulation.

Granting that pituitary extract is helpful in the majority of prolonged labors due to poor pains, there remains the paramount question as to whether or not its dangers are so great as to contraindicate use even in these difficult cases. In order to avoid the well-known risks of large doses for both mother and child, our patients were given small initial amounts so as to test out the reactivity of the uterine musculature, and subsequent doses as required were increased gradually. As noted before, we believe the first administration should perhaps not exceed 1 minim. Starting with 2 and 3 minims, a number of our patients (19) had strong pains immediately, though in only one was there excessive stimulation. After a 2 minim dose, this patient, a primigravida, had very strong and rapidly recurring uterine contractions with little relaxation. The alarming situation was relieved by the administration of ether anesthesia. Stimulation was only temporary, and fourteen hours later Dührssen's incisions and a midforceps delivery were done. Although there was no apparent damage done to mother or child, and although this is the only experience of the kind that we know of in this hospital, the incident shows that even a small dose is not free of all risk. The prompt effect of ether anesthesia in this instance, and on a similar occa-

TABLE II. CASE EFFICACY OF SMALL DOSES OF PITUITARY EXTRACT IN STIMULATING FIRST-STAGE LABOR PAINS IN PATIENTS WITH PROLONGED LABOR DUE TO UTERINE INERTIA

STIMULATION OF PAINS	PRIMIPARAS	MULTIPARAS	TOTAL CASES
Slight or temporary	13	7	20
Moderate	4	2	6
Strong	18	13	31
Strong with artificial rupture of the membranes	2	3	5
Total	37	25	62

Table II shows that in 20 of 62 cases there was slight or temporary, and, therefore, for the most part negligible, stimulation of the labor pains. In 6 others there was only moderate effect, yet from a review of the histories it was evident that the stimulated pains persisted and caused sufficiently progressive dilatation of the cervix as to consider the effect of the extract to have been definitely helpful or even satisfactory. In the next group of 31 the pains became strong and continued so until completion of the first stage. Though the last group is small (5 cases), it may be significant that in all these patients with employment of pituitary extract plus artificial rupture of the membranes there resulted strong and lasting pains. In 42 of 62 cases, with first-stage dystocia and prolonged labor due to uterine inertia, there occurred moderate to strong stimulation of uterine contractions up to complete dilatation of the cervix. The proportions for primiparas and multiparas were approximately the same, being 65 and 72 per cent, respectively. In this series we failed to find any reasons or associated factors, other than artificial rupture of the membranes in 5 cases, to explain why or how the administration of a substance with only a short pharmacologic action could cause lasting stimulation of uterine contractions. Nevertheless, from the clinical standpoint it is an important observation that such action was actually obtained in a substantial majority of our cases.

Although Table II indicates successful stimulation of pains in approximately 2 of 3 of these patients, the result when obtained did not follow a single administration or course of injections in all patients. In 3 primiparas and 8 multiparas two separate series of doses, and in one multipara 4 courses, were required for satisfactory effect. It is also true that repeat courses of the extract were unsuccessful in 6 primiparas and 2 multiparas. In Table III are given the results for the 84 individual series of injections, 62 being initial and 22 subsequent courses after an elapse of several hours or more. In addition to parity, there is also a tabulation of efficiency according to the degree of dilatation of the cervix.

In Table III no striking difference is noted for administration in primiparas or multiparas, the effect being definitely helpful or satisfactory in about 50 per cent in both. Approximately the same results were obtained in the different stages of dilatation of the cervix, with the exception of advanced dilatation in multiparas, where success was obtained in all. Here, however, the number involved (5) was too small for a trustworthy conclusion.

The foregoing data give, we believe, at least a conservative estimate, and probably an underestimate, of the beneficial results to be obtained in hastening dilatation of the cervix from careful administration of pituitary extract in uterine inertia. One of our standards for acceptance of a patient into the series was that labor should be prolonged for at least thirty hours. This restriction was intended to make certain that

were given two or more courses of repeated doses, good results for the individual courses being about 50 per cent. This percentage was approximately the same for primiparas and multiparas and also for different degrees of cervical dilatation, except for 6 cm. or more dilatation in multiparas where there was good effect in all 5 instances. In this series of 62 very difficult cases, intervention before full dilatation of the cervix was required in only 3, these being among those with only slight or temporary stimulation. That the method is not entirely free of danger is shown by the fact that there was one case of tetanic contraction of the uterus after a 2 minim injection without detectable injury to mother or child. Because of this experience and for other reasons, we recommend that the initial dose be no larger than 1 minim. One maternal death followed difficult operative delivery *after* full dilatation of the cervix and was not ascribable to use of pituitary extract in the first stage. The child in this case was subjected to craniotomy. Three other babies died in utero, but with evidence pointing to difficult labor rather than use of pituitary extract as the cause. There were no neonatal deaths or diagnosable birth injuries in the 58 babies born alive.

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DISCUSSION

DR. DAVID S. HILLIS, CHICAGO, ILL.—There are two things that are very much needed in obstetrics. One is an efficient and safe way to induce labor. Another is some successful method to manage the prolonged labor case. Personally, I would prefer to deal with any other complication in obstetrics than with a cervix which will not dilate. This is regarded as such an important question at Cook County Hospital that all prolonged labor cases are assigned to one attendant who gives each case his personal attention in an effort to learn the best method of dealing with this type of dystocia.

This in my opinion is an honest and intelligent contribution to our knowledge of the subject. The old method of using sedatives alone in prolonged labor has proved to be most unsatisfactory in a certain large proportion of cases. It is quite natural to turn to pituitrin as a drug which is known to increase some uterine activity and is the only agent which does this in a positive manner.

Pituitrin has a bad reputation because of the fact that it was seriously abused for many years after its introduction to the profession. Unfortunately, there is still some abuse of pituitrin. However, it is about time for the medical profession to learn to use a powerful agent such as this in an intelligent and conservative manner. It is not right that the profession should be deprived of the useful effects of a drug, properly used, just because some members of the profession abuse its use.

DR. RUDOLPH W. HOLMES, UNIVERSITY, VA.—I believe that pituitary extracts are highly dangerous to mother and fetus when injudiciously employed. Shortly after this drug became the obstetric panacea, it was exhibited promiscuously in heroic dosages with disaster. In those early days I collected 13 cases of uterine rupture in the Chicago area following the use of this drug, with the death of all

sion which one of us experienced in another hospital, lends support to DeLee's advice that a can of ether and a mask be readily at hand in these cases.

A review of the mortality in this series showed that there was one maternal death. We had some doubt about including this patient in the study since she had a contracted pelvis. So far as the first stage of labor was concerned, however, dystocia was apparently due to uterine inertia rather than cephalopelvic disproportion. In any event, at 8 cm. dilatation of the cervix 2 doses of pituitary extract (2 and 3 minims) gave good stimulation of the weak pains, so that the cervix was soon fully dilated. Descent of the head in the second stage came to a standstill at the level of the ischial spines. Four hours later an unsuccessful attempt at forceps delivery was followed by a difficult podalic version. Then, extraction was impossible, and craniotomy was necessary. The patient was in shock after delivery, but death twenty-two hours later came so suddenly as to suggest the possibility of pulmonary embolus. Viewed retrospectively, it appears that craniotomy immediately upon failure of forceps extraction, rather than another procedure, might well have had a different outcome for this woman. Certainly, there seems to be no reason for believing that administration of pituitary extract was in any way responsible for the regrettable result.

There were 3 stillbirths (and no neonatal deaths) in this series, besides the one due to craniotomy just mentioned. Two deaths occurred in primiparas, the fetal heart sounds disappearing approximately three hours and five hours after the extract was given. In both of these cases there was only fair or moderate stimulation of pains. The third death was in a multipara who had good stimulation of the pains but showed no suggestion in the record of tetanic contraction of the uterus. The exact time of death was not definitely stated. Evidently, 3 of the 4 dead fetuses in this series cannot be reasonably attributed to the effect of pituitary extract. The most that can be said for the fourth is that it was possibly due to the procedure, though the resulting uterine contractions were apparently no stronger than those that often occur in normal labor. Whatever the causes of the deaths, it seems fair to say that the gross fetal mortality of only 6.5 per cent in this small series gives no definite evidence of increased risk from the administration of pituitary extract. Indeed, considering the fact that these were very difficult cases, it may be justifiable to say that the relatively low mortality indicates the reverse.

SUMMARY

Although large injections of posterior pituitary extract are admittedly dangerous when given in labor, this does not mean that small doses cannot be given with reasonable safety and advantage in prolonged first stage of labor due to poor labor pains. In 62 such cases (definitely in labor at term and with normal children) there was efficient and lasting stimulation of pains in 42. Five patients given pituitary extract plus artificial rupture of the membranes had good stimulation. Some patients

THE RELATIVE EFFECT OF ANALGESIA AND ANESTHESIA IN THE PRODUCTION OF ASPHYXIA NEONATORUM*

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IN VIEW of the widespread use of drugs and anesthetics to relieve the pain of childbirth, not only by specialists but also by general practitioners as well, there has been an understandable critical scrutiny of the results of this practice. Since the introduction of barbiturates, there have been numerous papers which extol the benefits of these drugs either alone or in combination with scopolamine, but most of them deal only in general with results as far as the babies are concerned. Physicians have been taken sharply to task for predelivery medications by such observers as Henderson and Schreiber. Henderson,¹ for example, states that 30 to 60 per cent of babies delivered under analgesics are born asphyxiated and need some method of resuscitation, while Schreiber² states that as a result of asphyxia at the time of birth many babies suffer from permanent cerebral damage.

If these statements are borne out by further investigation, it will be obligatory for us to discontinue the use of sedatives. Recently, there have been investigations which have led us to believe that general anesthesia is also to blame for increasing the incidence of asphyxia of the newborn.³

In order to shed a little light on what is a seriously controversial subject, we undertook this investigation. Variables have been eliminated as far as possible. All deliveries were made by one of us (H. H.). These are consecutive deliveries over a period of about two and a half years. The analgesics used were sodium pentobarbital 3 to 6 grains, reinforced by scopolamine. In practically all instances enough analgesia was used to produce complete amnesia from the time the effect was produced until after the baby was born. In the local anesthesia 1 per cent novocain was used either by pudendal block or by perineal infiltration. A few of the more complicated deliveries were given intradural block. In the general anesthesia group drop ether was used in about one-half of the cases, and nitrous oxide and ether in the rest. The latter were given oxygen in sufficient quantity to keep the patient pink. The babies were all handled in the same way. After birth the child's air passages were cleared by milking the trachea and wiping out the mouth. No other stimulation was used. The cord was not cut until respiration was established or until definite asphyxia was diagnosed. If the child failed to breathe or gasped sluggishly, the air passages were cleared with a tracheal catheter and oxygen with 5 per cent carbon dioxide was given with an inhalator. Failing these methods, artificial respiration was then instituted.

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mothers and their babies. It is an inexcusable blunder to give full ampoule dosages to stimulate uterine contractions. Fractional amounts in selected cases may be of inestimable value. I believe Hofbauer's nasal administration is the preferable method, for if untoward signs begin to develop the nasal pledget may be readily removed.

In normal vertex presentations at the time "lightening" occurs, there is a fair contact between the head and the girdle of the lower uterine segment. As a result of this pressure a progressively increased intensity and frequency of contractions develops. When there is any interference with the adaptation of the presenting part, labor is almost always accompanied by weak, ineffectual contractions in the first stage. As example of such conditions I would cite pelvic asymmetry or contraction, abnormal presentations and placenta previa. All of these are accompanied by the classic ineffectual, nagging contractions, with a prolongation of the first stage, called by the earlier writers *dolores presagientes*. It is a difficult matter to differentiate between such false pains and the so-called primary inertia. Believing these precepts, I rarely used fractional doses of pituitrin to stimulate contractions during the early part of such labors. In selected cases the extract from the posterior lobe is of great value. Ordinarily, allowing the woman to change her position in bed, to walk about, and even giving her chloral hydrate and sodium bromide are of help. I have seen such fetal disasters follow the administration of morphia in labor with resultant prompt termination of labor that for years I had practically prohibited its use in my services.

In conclusion, I believe that Doctors Siddal and Harrel have shown a rare circumspection in employing those fractional doses of the pituitary gland extracts in a selected few distinctly abnormal cases culled from the large series of patients their clinic has attended. If their conservatism were general in the profession we would have no rabid strictures against the use of this indispensable drug. The use of it is invaluable, its abuse an abomination.

DR. GERALD W. GUSTAFSON, INDIANAPOLIS, IND.—It would be very interesting, particularly as this work was done in Detroit, to have Dr. Schreiber study these babies to find whether he could detect any evidence of areas of cerebral degeneration.

I believe there is only one real indication for pituitrin while the baby is still in the uterus, and that is in the treatment of the worst cases of abruptio placentae. A few years ago we all taught radical treatment for these cases. Last week in my service in the Indianapolis City Hospital we had a chance to see what conservative treatment could do. The woman was a para iii who came in in tremendous shock. After giving two or three transfusions, she was given 1 minim of pituitrin, the membranes were ruptured, a Spanish windlass was applied, and she went into labor. She delivered a stillborn baby normally. I was very skeptical about this particular type of treatment after hearing DeNormandie telling of their success in the Boston Lying-in Hospital, but I am convinced that many more mothers will be saved by its adoption.

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—What type of syringe is used when you inject one minim of pituitrin?

DR. SIDDALL (closing).—We use a tuberculin syringe for giving pituitrin. I do not believe there is any other syringe by which you can accurately measure dosage.

Pituitrin has been badly abused and we do not want to repeat those instances. However, from our experience we still believe that the drug has a place in a certain number of cases. I cannot conceive our giving up the use of this aid in patients, such as those of this series, who really need its help.

We have assigned a minimal asphyxia value on spontaneous delivery, spontaneous breech, and prophylactic forceps. For the purpose of this paper, delivery by cesarean section has not been considered. Forceps delivery, versions and extractions, and breech extraction are assigned a high asphyxia value. The increase of asphyxia in prolonged labor and lengthy anesthesia has been shown graphically by Cole, Kimball, and Daniels, and this we have taken into account. Prolonged labor and anesthetics are similarly treated. We have considered analgesia in three groups: first, less than enough to produce full analgesia; second, full analgesia; and third, prolonged complete analgesia. Spontaneous onset of labor has a minimum asphyxia value. Medical induction is given an increased value and surgical induction a further increase. Bag induction is given the highest asphyxia value on account of increased cerebral pressure produced by this mechanical device.

Eastman has shown that the fetus lives in utero in a state of mild asphyxia.⁵ There is no true arterial blood in the fetus. The fetal arterial blood has a lower oxygen saturation than the venous blood of the mother. This is partially compensated for by the higher oxygen carrying power of the newborn, since the average fetal hemoglobin concentration is 112 per cent while that of the mother is only 84 per cent.

TABLE II. OXYGEN SATURATION (AFTER EASTMAN)

MATERNAL BLOOD %		FETAL BLOOD %
Arterial	95	63 (in utero)
Venous	71	50 (at birth)
		20-25
No analgesia or anesthesia		

Snyder and Rosenfeld⁷ showed that fetal respiration in utero is the rule and that these movements are not initiated at birth but are merely amplified with the result that air is introduced into the lungs at the birth of the child. Clifford and Irving⁸ showed that these prenatal respiratory movements are slowed or stopped by the exhibition of certain drugs and anesthetics.

This new knowledge of the physiology of respiration has been generally accepted, although positive proof in the human being is still lacking. Accepting these findings makes us ask ourselves whether or not it is dangerous to the child to suppress these respiratory movements. If analgesia and anesthesia depress this function, their combined use should increase the incidence of asphyxia. As practical obstetricians we are loathe to give up analgesia, and the question arises in our minds, "What effect will the elimination of anesthesia have on the incidence of asphyxia?"

Clinically, analgesia does not decrease the oxygen content of the mother or the fetus. Patients are often restless, their pulse is elevated, and their skin is flushed, but they do not become cyanotic under doses that produce amnesia. Therefore, these drugs increase asphyxia by respiratory depression and not by intrauterine asphyxia. We believe then that barbiturates and scopolamine will not affect the oxygenation of the child as long as the placental circulation persists. If serious respiratory depression from drugs exists, then asphyxia will develop

These two groups, then, eliminate the variables which can arise from difference in technique and training of the obstetrician. There always has been and still is a variation due to observation, and, for this reason, we established a classification of asphyxia different from that in common use.

We classify five groups of respiratory response as indicated in Table I. In this classification individual judgment is eliminated. Groups 1 and 2 can be classified as normal, while Groups 3 and 4 are definite asphyxia, differing only in degree.

TABLE I

Group 1.	Babies that breathe within ten seconds. These infants usually cry with the first expiration.
Group 2.	Babies that breathe between eleven and thirty seconds after birth. They also cry quickly as a rule.
Group 3.	The initial respiration is delayed thirty seconds or more. An infant which breathes earlier than thirty seconds and lapses into apnea is classed in this group. These babies are easily revived with tracheal catheter and oxygen.
Group 4.	Babies in whom the above measures fail and artificial respiration is necessary.
Group 5.	Stillborn.

We believe that this classification, at least for investigative purposes, is better than the division into asphyxia livida and asphyxia pallida. Both, it is true, are clinical classifications, but we feel that ours is the more exact. We also discarded the method of Cole, Kimball, and Daniels,⁴ in which the degree of asphyxia was based on the number of methods of resuscitation used. As has been pointed out by others, a nervous operator may institute such measures earlier than a more phlegmatic obstetrician.

Many factors exist during labor which tend to produce asphyxia, and long before the advent of analgesia and anesthesia asphyxia neonatorum held a prominent place in the writings of obstetricians. Prolapsed cord, abruptio placentae, placenta praevia, dystocia, and occult cord pressure are conditions that are not completely under our control. Analgesia and anesthesia, however, are controllable. By painstaking observation and accurate reporting we can arrive at a formula which does not increase the hazard of birth.

All drugs and anesthetics must by their very nature cause depression of vital functions including the respiratory center. It is not our purpose to deny this. The amount and significance of this depression have been exaggerated by some and minimized by others. If reasonable relief of pain can be secured by medications now at our disposal, we are thoroughly justified in their use. If modification of our present methods of using these drugs will decrease the danger to mother and child, we must make these changes.

In this study all factors are considered which may increase the normal condition of mild asphyxia. Asphyxia values are arbitrary and undoubtedly erroneous in many cases, but in the aggregate they probably give a reasonably true estimate of their influence in the production of anoxemia.

TABLE IV. SUMMARY OF ENTIRE GROUP

	Total number of Cases	975	
Group 1	714 cases	73.2%	90.6%
Group 2	179 cases	17.4%	
Group 3	51 cases	5.2%	6.5%
Group 4	13 cases	1.3%	
Group 5	18 cases	1.9%	
90.6% show no asphyxia			
6.5% are asphyxiated			

When these figures are broken up into local and general anesthesia, we find that 95.4 per cent of the cases of those given local anesthesia were normal and 3.7 per cent were in a varying state of asphyxia. The asphyxia rate under general anesthesia is 9 per cent. Attention is called, however, at this point to the fact that the increase is entirely in the group of asphyxia livida (Group 3) because the incidence of Group 4 asphyxia is identical; namely, 1.3 per cent.

TABLE V. CONDITION OF INFANT AT BIRTH

A. General Anesthesia				
Total cases—524				
Group 1	361 cases	68.9%	}	88.3%
Group 2	102 cases	19.4%		
Group 3	40 cases	7.7%	}	9.0%
Group 4	7 cases	1.3%		
Group 5	14 cases	2.7%		
B. Local Anesthesia				
Total cases—451				
Group 1	353 cases	78.3%	}	95.4%
Group 2	77 cases	17.1%		
Group 3	11 cases	2.4%	}	3.7%
Group 4	6 cases	1.3%		
Group 5	4 cases	0.9%		

In Table VI the cases of asphyxia livida (Group 3) are analyzed. In the general anesthetic group of 40 cases there were possible etiologic factors noted in all but 13. When one remembers that occult cord pressure undoubtedly occurs frequently, this is not an unreasonable proportion. In the local group of 11 cases no cause is noted in 5 instances. Two cases are listed under aspiration of amniotic fluid. The possible effect of analgesia in producing this condition cannot be ruled out.

TABLE VI. SUMMARY OF CASES IN GROUP 3 (ASPHYXIA LIVIDA)

A. General Anesthesia (40 cases)	
No cause noted	13
Dystocia	7
Induction of labor	6
Coil of cord around neck	5
Prematurity	4
Partial premature separation of placenta	3
Breech	2
B. Local Anesthesia (11 cases)	
No cause noted	5
Partial premature separation of placenta	2
Aspiration of fluid	2
Pre-eclampsia (induction)	1
Prematurity	1

as the placental circulation ceases. It is the object of this paper to throw some light on this question.

It might be well to recall at this point that the role of carbon dioxide in the stimulation of the respiratory center was the contribution of Yale's physiologist, Yandell Henderson, and it was he who first advocated use of oxygen-carbon dioxide mixtures to counteract this condition. Independently from this discovery, but almost simultaneously, the attitude of obstetricians changed from back slapping and hot and cold tubbing to one of gentleness and conservation of body heat, an attitude which today is more widespread and firmly grounded than ever.

Recently, Snyder and Rosenfeld showed that nonvolatile drugs, including all the commonly used analgesics, depressed or completely stopped intrauterine fetal respiratory movements. Similar findings were noted in nitrous oxide anesthesia, to a less extent following the use of ether, and not at all with cyclopropane.

In 1936 Eastman⁶ published experiments indicating that chloroform has no appreciable effect on fetal oxygen concentrations, while ether reduced the saturation to 45 per cent in the arterial blood and to 15 per cent in the venous blood. Nitrous oxide-oxygen anesthesia shows an even greater reduction in the oxygen saturation of the fetal blood.

TABLE III. EFFECT OF ANESTHETIC ON OXYGEN SATURATION IN FETAL BLOOD AT BIRTH (AFTER EASTMAN)

	ARTERIAL %	VENOUS %
No anesthetic	50	20
Chloroform	No appreciable effect	
Ether	45	15
Nitrous oxide (80-20)	40	10
(90-10)	25	0.5

From the work of Snyder and Rosenfeld it appears that analgesics depress the respiratory center of the fetus but no proof is offered, and clinical observations indicate that drugs used in the first stage in moderate dosage have no effect on the oxygen saturation of the fetal blood. Anesthetics on the other hand, especially nitrous oxide, definitely lower the oxygen saturation of the fetal blood.

Little notice was taken of the possible late effects of asphyxia neonatorum until Schreiber called attention to a group of young children with late neurologic symptoms.² He reports that 70 per cent of a series of 500 cases showed some degree of apnea at birth. While he blames precipitate delivery, breech extraction, other forms of dystocia, and prematurity for many of these defects, he also indicts the use of analgesic drugs as a factor in the production of these late neurologic conditions. Whether one agrees with him in the entirety of his contentions or not, it makes us pause and re-evaluate our methods.

MATERIAL

In this report we have tabulated the results of 975 consecutive deliveries by one of us (H. H.), studying each case from the standpoint of all factors to which we may assign an asphyxia-producing value. Of these deliveries, 524 were made under varying degrees of analgesia plus whatever anesthesia was necessary to complete the delivery. A total of 451 babies were delivered under analgesia plus local anesthesia. The condition of the infant is tabulated in Table IV. Six and five-tenths per cent of all babies showed some degree of asphyxia, 90.6 per cent may be classified as normal, while 1.9 per cent were stillborn.

Table IX lists the cases of mild and extreme analgesia. It must be noted that the cases of analgesia degree three were long, hard, complicated labors. Yet as the table indicates there was essentially no difference in the condition of the babies at birth.

Inasmuch as the general anesthesia group shows a somewhat higher incidence of asphyxia than does the local group, the question arises as to the effect of operative procedures. Under pudendal block or infiltration anesthesia, it is difficult

TABLE IX. LOCAL ANESTHESIA

A. Analgesia degree 1 (mild)				
Total cases		40		
Condition of baby				
Group 1	22	73.3%	}	96.6%
Group 2	7	23.3%		
Group 5	1	3.3%		
B. Analgesia degree 3 (extreme)				
Total cases		53		
Condition of baby				
Group 1	37	69.8%	}	96.2%
Group 2	14	26.4%		
Group 3	1	1.9%		
Group 5	1	1.9%		

TABLE X. CONDITION OF BABY FOLLOWING OBSTETRIC OPERATIVE PROCEDURE OTHER THAN PROPHYLACTIC FORCEPS AND SPONTANEOUS BREECH DELIVERY

A. General Anesthesia (122 cases)				
(1) Midforceps	39 cases			
22 cases	Group 1	56.4%	} 84.6%	
11 cases	Group 2	28.2%		
4 cases	Group 3	10.4%		
1 case	Group 4	2.5%	} 13.9%	
1 case	Group 5	2.5%		
(2) Breech extraction and version	79 cases			
52 cases	Group 1	66%	} 90%	
19 cases	Group 2	24%		
6 cases	Group 3	7.6%		
0 cases	Group 4	0	} 7.6%	
2 cases	Group 5	2.4%		
(3) Dührssen's incision and forceps or version	4 cases			
2 cases	Group 1			
2 cases	Group 2			

TABLE XI

B. Local Anesthesia (62 cases)				
(1) Midforceps	32 cases			
28 cases	Group 1	87.5%	} 93.8%	
2 cases	Group 2	6.3%		
1 case	Group 4	3.1%		
1 case	Group 5	3.1%		
(2) Breech extraction and version and extraction	25 cases			
20 cases	Group 1	80%	} 96%	
4 cases	Group 2	16%		
1 case	Group 4	4%		
(3) Dührssen's incision and forceps or version	5 cases			
2 cases	Group 1			
2 cases	Group 2			
1 case	Group 5			

In Table VII the cases classed as Group 4 (asphyxia pallida) are analyzed. In the general anesthetic group of 7 no cause is noted in 5. One case terminated in a midforceps operation and one was complicated by a long induction in a nephritic toxemia, with no analgesia and a minimum of anesthesia. In the local anesthesia group we find a partial premature separation of the placenta, a tight coil of cord around the neck, a breech delivery, a midforceps operation, and a case of aspiration of amniotic fluid. The sixth case was noteworthy. The patient had a previous cesarean section and when labor began had a fulminating pneumonia. She was sectioned under sodium pentothal and abdominal block anesthesia. She died within twenty-four hours with complete consolidation of both lungs. The baby, however, was resuscitated and at present is living and well.

TABLE VII. SUMMARY OF CASES IN GROUP 4 (ASPHYXIA PALLIDA)

Total number of cases	13
General Anesthesia	7
No cause noted	5
Midforceps	1
Nephritic toxemia	
Bag induction	
No analgesia	1
Minimum anesthesia	
Local Anesthesia	6
Fatal maternal pneumonia	1
Sodium pentothal and local abdominal block	
Midforceps	1
Partial premature separation of placenta	1
Breech delivery (aspiration of fluid)	1
Tight coil of cord around neck	1
Aspiration of amniotic fluid	1

Table VIII classifies the stillborns. The data are self-explanatory and the only case needing clarification is the one listed as general hypoplasia. This child at post mortem showed craniotabes and a general lack of development, which probably accounted for its death. The heart was beating when born, but there was no attempt at respiration despite the exhibition of stimulants and artificial respiration. It is noteworthy that among these 18 cases there were none which could be classified as deaths resulting either from delivery or from the use of analgesic or anesthetic drugs.

TABLE VIII. SUMMARY OF CASES OF GROUP 5 (STILLBORN)

Total number of cases	18
Macerated fetus	5
Monstrosities	5
Fetal heart lost early in labor (cord pressure?)	3
Premature separation of placenta	1
Erythroblastosis	1
Extensive placental infarction	1
Craniotabes and general hypoplasia (autopsy)	1
Premature (26 weeks)	1

The cases of local anesthesia were further broken down into, first, those receiving insufficient analgesia to produce amnesia; second, those receiving full analgesia; and third, those receiving heavy doses of analgesia. Full analgesia was considered as being 6 grains of nembutal and 2 one-hundredths to 3 one-hundredths grain of scopolamine. An amount less than this is called analgesia degree one; an amount greater is designated as degree three.

2. Causes other than the use of analgesia or anesthesia are found in two-thirds of the cases that are clinically asphyxiated and may be present in others.

3. General anesthesia definitely decreases the respiratory response of the newborn.

4. The percentage of asphyxiated babies of amnesic mothers delivered under local anesthesia is comparable to the percentage expected when unnarcotized mothers are delivered under light ether or chloroform anesthesia.

5. When properly supervised and in the hands of those familiar with their use, analgesics per se do not increase the incidence of asphyxia.

6. Neither anesthesia nor analgesia, properly controlled, need be a factor in the production of stillbirths.

7. In the majority of cases asphyxia neonatorum is due to interference with the transfer of oxygen from the maternal blood to that of the fetus.

8. The use of local anesthesia whenever possible will reduce the natural hazard of birth.

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3001 WEST GRAND BOULEVARD.

DISCUSSION

DR. GERALD W. GUSTAFSON, INDIANAPOLIS, IND.—For years we have known that certain conditions would produce anoxemia in the infant. Of these, compression of the cord and abruptio placentae are the most common, but with very hard pains anoxemia may also be produced. Here the circulation through the placenta is so seriously compromised and the interchange of gases rendered so difficult that the fetal blood cannot be oxygenated. Under this circumstance, analgesia and anesthesia may actually benefit the fetus by decreasing the anoxemia. The significance of fetal respiratory-like movement is not agreed upon by physiologists, since Windle of Northwestern believes that under normal physiologic conditions the fetus is apneic and only develops respiratory movements in the presence of anoxemia.

It is a well-known fact that in the presence of extreme anoxemia, living cells degenerate. Schreiber has called attention to the possibility that unpharmacologic dosage of analgesia may produce this degree of anoxemia in the brain. This subject is, therefore, of increasing importance to the obstetrician, and it is up to us to show that our methods of analgesia not only are not destroying babies but likewise are not permanently injuring them from a neurologic standpoint. In a recent paper, Dr. Garceau and I showed that many cases of cerebral spastic paralysis, where marked cerebral injury was present, breathed spontaneously at birth without clinical evidence of asphyxia.

Until more investigation is done, the obstetrician should practice and teach a middle ground of analgesia. It seems to me that Dr. Henderson has done just that, for only 53 of his 975 cases had what he describes as extreme analgesia. His stillbirth record of 1.9 per cent, or 18 cases, in 975 deliveries is excellent, the stillbirth record in the United States for 1936 being reported as 34 per 1,000. None of his stillbirths could be classified as resulting from delivery or from use of analgesia or anesthesia. That 90.6 per cent of his babies breathed within thirty seconds indicates very little anoxemia in the entire group. Our experience with

to do hard obstetric operations, and many of our complicated cases were given ether or nitrous oxide-ether for this reason. Table X lists a total of 122 cases in which major obstetric procedures were done, together with the incidence of asphyxia. Table XI shows 62 cases of dystocia delivered under local anesthesia. Table XII summarizes this information, with a comparison of the results in the entire group.

TABLE XII. SUMMARY OF CASES OF DYSTOCIA

A. General Anesthesia									
Entire group (524 cases)				Dystocia only (122 cases)					
Group 1	361	68.9%	88.3%	76	62.3%	88.6%			
Group 2	102	19.4%		32	26.3%				
Group 3	40	7.7%		10	8.2%				
Group 4	7	1.3%	9%	1	.8%	9%			
Group 5	14	2.7%		3	2.4%				
B. Local Anesthesia									
Entire group (451 cases)				Dystocia only (62 cases)					
Group 1	351	78.3%	95.4%	50	80.6%	93.6%			
Group 2	77	17.1%		8	13.0%				
Group 3	11	2.4%		0	0.0%				
Group 4	6	1.3%	3.7%	2	3.2%	3.2%			
Group 5	4	0.9%		2	3.2%				

SUMMARY

A series of 975 consecutive unselected deliveries by one operator are analyzed from the standpoint of factors which might produce asphyxia in the newborn. A slight preponderance of deliveries under general anesthesia was noted. Of the entire group 90.6 per cent required no resuscitation. Five and two-tenths per cent were revived simply by aspiration of the trachea and the administration of oxygen and 5 per cent carbon dioxide. One and three-tenths per cent required artificial respiration, and 1.9 per cent were stillborn. None of the 18 stillbirths could be attributed to the means of delivery or the use of either analgesics or anesthetics.

A total of 95.4 per cent of those in the local anesthesia group and 88.3 per cent of the general anesthesia group breathed spontaneously. Severe asphyxia occurred in the same percentage in the entire series; namely, 1.3 per cent. The chief difference between general and local anesthesia lies in Group 3 (asphyxia livida).

Reasonably definite causes of the asphyxia can be shown in about two-thirds of all cases of delayed respiration other than the exhibition of analgesics or anesthetics.

Among the local anesthetics there was no difference in the respiratory response whether analgesia was insufficient to produce amnesia or whether it was prolonged beyond the degree usually found sufficient to result in amnesia in the average normal labor.

In this series dystocia by itself apparently had no influence on asphyxia.

CONCLUSIONS

1. Ninety and six-tenths per cent of babies born when the mother is under the influence of analgesia show no evidence of clinical asphyxia.

thesia was used. However, the patients are frequently restless, and it takes a trained hospital personnel to carry out the technique properly.

Dr. Galloway brought out the point that 2 per cent of all babies are born mentally deficient whether they have analgesia or not. Anoxemia may be a factor in these 2 per cent, but congenital defects of the brain and encephalitis acquired after birth, without doubt, account for many of them.

Dr. Schreiber has at least brought to our attention the possible danger of anoxemia, and this paper indicates in what way we may reduce asphyxia in the newborn without losing the desirable effects of carefully controlled analgesia.

CONGLUTINATIO ORIFICII EXTERNI AS A FACTOR IN DELAYED LABOR*

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ACCORDING to Gugisberg and Kraatz (cited by Katsu¹), the incidence of the condition known as *conglutinatio orificii externi* is from 0.1 to 0.2 per cent; Zweifel (also cited by Katsu) found only 20 cases in the medical literature prior to 1873. On the other hand, this complication of labor is by no means as infrequent as it is generally supposed, for I have personally seen 3 cases in the last nine years, 2 of which occurred within the last eighteen months.

A survey of the medical literature has revealed only 28 articles on this subject from 1859 to date. All but 2 (Himmelsbach,² 1904; Porter,³ 1910) are in the foreign literature, and most of these consist of only a few pages, devoted chiefly to case reports. The condition is mentioned briefly in Williams'⁴ and DeLee's⁵ textbooks, but most other textbooks of obstetrics ignore it completely. For this reason, I feel justified in calling attention to cervical conglutination as a possible cause of delayed labor and in putting on record 3 typical cases.

In order to comprehend the basic pathology of this condition, it is necessary to recollect the normal anatomy of the cervix. The outer longitudinal layer of muscle, which covers the uterine corpus and fundus, the broad, round, ovarian, and uterosacral ligaments, and the Fallopian tubes, stops short of the cervix. The cervical musculature consists chiefly of circular and oblique bundles, intermingled with a considerable amount of dense fibrous and elastic tissue, the structure accounting for the resistance and hardness typical of the cervix (Piersol⁶). When cervical conglutination is present, a few of the circular fibers around the external cervical os fail to dilate, although the effacement of the cervix, which is part of the physiologic process of labor is complete. They become thinned out by the bulging intact membranes or the advancing head, and the presenting part is separated from the vaginal canal only by a thin layer of cervical tissue, but they do not dilate and dystocia necessarily results. It is obvious, however, that the condition is not a true conglutination, as it was once believed to be, and that it should be given a new and more correct name.

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block anesthesia, though small, coincides with his, since babies from mothers having block anesthesia breathe a trifle sooner than those delivered by general anesthesia.

My personal preference has been to supplement 6 grains of nembutal when necessary with rectal ether instead of scopolamine. In slightly more than 1,000 private cases using this method, no stillbirth attributable to analgesia has occurred.

DR. GEORGE KAMPERMAN, DETROIT, MICH.—All of us in Detroit were put on the defensive by the work of Schreiber, when he pointed out that damage to the brain could occur by anoxemia, and we could not refute the argument. That is one of the reasons why Dr. Henderson has undertaken this work.

I have not used much local anesthesia. I have practically given up nitrous oxide and have resorted to the use of ether when we do need an anesthetic. I believe that the ordinary anesthetist when she gives nitrous oxide is quite apt to give too little oxygen. We specify that we want 20 per cent oxygen, but the anesthetist often gives less, I am sure. It is hard for the operator to know just how much oxygen the patient is receiving.

As Dr. Gustafson said, I think the middle of the road in analgesia is still the proper thing. Personally, I think we should train our patients not to expect a painless labor. We should not tell them we will meet them at the front door with an analgesia. They should expect to go through part of the labor before analgesia is given. In this way a minimum of analgesia is needed to relieve the patient. Most patients can cheerfully endure the early labor pains. If we delay giving analgesia until dilatation of the cervix has well started, then usually one dose will carry the patient through the remaining labor. The amount that is given is exceedingly important.

DR. CHARLES EDWIN GALLOWAY, EVANSTON, ILL.—Since the world began about 2 per cent of the population has been born mentally deficient, and for someone to go into an institution and pick out several hundred cases and make the statement that the majority of them did not breathe very well at birth is not very scientific evidence that asphyxia is the cause of the brain injury. I discussed a paper concerning this subject when it was read in San Francisco and I am still of the same opinion. Apparently there is not much ill effect to either mother or baby when it comes to the matter of trying to relieve the pain of labor. I investigated all cases in my own community and asked each pediatrician and every psychiatrist whether analgesia in labor had anything to do with the mental deficiency of the children. We could not discover one case of mental deficiency in a child which could be attributed to the use of drugs at birth.

Each time an advance is made in the practice of medicine, certain problems have to be met. We are now trying to work out some of these problems. There are a few men among us who would much prefer to toss the problem out the window rather than to try to reach a solution. For instance, in the case under discussion, it is no solution to this problem simply not to administer drugs or anything to relieve the patient's pain. We should do as Dr. Henderson has done—work it out. If a baby is asphyxiated, then counteract the asphyxia immediately. We should strive to practice conservative medicine by administering only enough drug for pain relief and not too much as some physicians are now doing.

It is interesting to note that some of the men who are disparaging the use of analgesia are the very ones who have advocated it for years; they have even shown themselves in motion pictures administering morphine and scopolamine for their teaching. I believe that obstetricians all over the country are trying to relieve the pain of childbirth and that the individual obstetrician should not be discouraged, but rather encouraged, to continue on a rational basis with his effort.

DR. HENDERSON (closing).—Local anesthesia with moderate sedation can be used by the general practitioner, but as employed in this series it is undoubtedly inapplicable to the man who does an occasional case. Not once in the series given local anesthesia was there a serious post-partum hemorrhage; only one patient vomited, and this was due to fundus pressure when a large pair of shoulders impeded delivery. The patients all reacted more quickly than when general anes-

is instituted. Obliteration of the cervix is part of the normal process of labor, and attempts at manual dilatation, cervical incision, introduction of bags, and similar measures merely create complications and are to be condemned. In a few instances, if labor is permitted to continue normally, dilatation of the external os will occur spontaneously, but in most instances artificial measures must be employed because of the risk of additional dystocia as the result of edema of the cervix, or because of the possibility of traumatic amputation of the cervix or rupture of the uterus.

The simplest measure to relieve the conglutination is continued gentle, steady digital pressure upon the depression which represents the external os. As a rule, such pressure is immediately successful, the finger promptly enters the cervical canal, further dilatation occurs at once, and delivery follows immediately and sometimes almost precipitately. Traumatic manipulations should be avoided. If the finger does not enter the canal promptly by the use of a minimum degree of force, manual dilatation may sometimes be employed cautiously, but both manual and instrumental dilatation are open to the same objections, that uncontrolled tears may result from their use, and controlled crucial incisions into the cervical tissue are usually more satisfactory.

When the cervical conglutination is due to previous treatment with caustics or previous operative procedures, the location of the depression which represents the external canal may be difficult if not impossible, and the stenosis may be of such a degree and type that delivery from below might be attended with disaster. Stander (in his revision of Williams' text) has reported several cases following high amputation of the cervix in which the uterus was extirpated at cesarean section and no trace of the opening could be found, though the external os must unquestionably have existed for conception to have occurred. Under such circumstances cesarean section is probably the safest as well as the most conservative mode of delivery.

The successful outcome of the unusual case reported by Himmelsbach makes it worthy of citation. Amputation of the cervix was unwittingly done during pregnancy because the patient gave an untrue history. The presentation was breech. Engagement and effacement of the cervix was present, following abortive labor pains a week before the two-day labor ensued, which finally terminated in delivery by forceps following manual dilatation of the external os. The mother made a smooth recovery and the child survived, though resuscitation was accomplished with some difficulty.

CASE REPORTS

CASE 1.—Mrs. B., a white female, aged 28 years, para i, gravida ii, menstruated for the last time May 28, 1932, and expected delivery March 4, 1933. Her pregnancy was normal throughout and she presented no pelvic disproportion.

Her previous history was without incident, except for a perineorrhaphy and curettage of the uterus one year before the inception of the present pregnancy.

Labor began at 8 A.M. March 19, 1933. The position was L.O.A. The pains were strong and regular from the onset. Vaginal examination at the end of two and a half hours revealed effacement of the cervix to be progressing normally, al-

Although cervical conglutination, according to the reported cases, may occur in either primiparas or multiparas, it does not tend to recur in subsequent pregnancies. In certain instances the cause of the condition is clear; in others it is entirely speculative. The various causative factors established or suggested include:

1. The effect of the performance of plastic or mutilating operations upon the cervix.
2. The effect of the use of topical cervical applications or of corrosive substances, either for douches or in the attempt to produce an abortion.
3. Stenosis of the cervix following difficult labor.
4. Ulceration and induration as the result of syphilitic infection of the cervix.
5. Adhesions of the membranes about the internal os, with resultant prevention of the free action of the dilating fibers.
6. A predominance of fibrous tissue in the structure of the cervix.

Although the cause of cervical conglutination is not always clear, the clinical effects are always characteristic. In the usual case the position and presentation offer no obstacles to delivery, engagement occurs as in normal labor, and the pains are usually regular and strong. In short, there is no reason to suspect that delivery will not occur spontaneously and promptly. No progress, however, seems to occur beyond a certain point. Examination reveals that, although obliteration of the cervix is almost or entirely complete, dilatation of the external os has not occurred, and the thinned out and obliterated cervical tissue fits like a cap over the bag of waters or the fetal head.

If the condition is not recognized, the cervix is likely to become edematous from disturbance of the circulation. It may be delivered externally, still covering the fetal head (DeLee), or it may be torn off (Jentzen, cited by Porter). In some of the reported cases the uterus was ruptured.

The opening in the external os may be felt only as a tiny, pin-point depression, where the os would normally be located. Even by speculum examination it is sometimes impossible to identify the location, though usually a tiny hole is seen surrounded by a very red ring (DeLee). In the case reported by Porter, examination by speculum revealed a small stream of meconium emerging from a depression in the cervical tissue, through which, when the meconium was wiped away, a few long black hairs emerged. Such an aid to identification is, however, unique. As a rule, one must depend for diagnosis upon the digital identification of the sunken, depressed, nonresistant area which represents the external os and which is distinctive and different from the surrounding tissue, or upon its identification by speculum. Most often the direction of the depression is toward the vaginal fossa, but Katsu and Himmelsbach both call attention to the confusion which may occur when the cervix is displaced, as it was in Katsu's case, in which the external os was markedly retrodisplaced.

Cervical conglutination is usually not recognized until labor has progressed to a considerable degree. If it should be recognized early, full obliteration of the cervix should be permitted to occur before treatment

2. The term is a misnomer, since the condition is not a true conglutination, but rather a failure of dilatation of the circular fibers around the external cervical os.

3. The clinical picture is usually typical. The opening in the cervical os cannot always be identified even by speculum examination.

4. Artificial measures are usually necessary to relieve the condition, which sometimes terminates in spontaneous delivery, but may result in prolonged dystocia, amputation of the cervix, or rupture of the uterus. Usually all that is necessary is entrance into the cervical canal by continuous gentle digital pressure against the external os. Cesarean section is occasionally required.

5. Three typical cases are reported.

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DISCUSSION

DR. RUDOLPH W. HOLMES, UNIVERSITY, VA.—The earlier authorities described two types of conglutination: one where there was merely a constriction (stenosis) of the external os and failure of dilatation; the other where there was an actual agglutination of the external os with absolute obliteration of the lumen. In numerous instances I have found that the former may be adequately treated by the simple rupture of the membranes. In actual agglutination, where there is no opening, some form of cutting must be employed. As cervical effacement is extremely developed in both types I have always taught that Dührssen's incisions are far preferable to cesarean section.

DR. ALFONS R. BACON, CHICAGO, ILL.—Only a few months ago we had a patient with this condition at the Municipal Tuberculosis Sanatorium.

Mrs. G. F., a primipara, began labor on a Friday afternoon and simultaneously reported leakage of liquor amnii. During Friday night, and on Saturday and Sunday she had pains of fair quality which continued until Monday morning when there was a diminution of the pains. The doctors on service made five rectal examinations, from which they reported early progress in the descent of the head to a level below the ischial spines; they also reported that they thought the cervix was completely dilated.

When I was called for vaginal examination I found that the cervix was quite thin and the external os was closed except for 1 to 2 mm. By a boring motion it was possible to get through the os, then the dilation proceeded more easily and the os was finally dilated to 5 or 6 cm. The fetal heart tones were elusive, and there was some doubt as to their existence, the patient was somewhat weakened from the long three-day labor. Dührssen's incisions were made anteriorly and posteriorly, and forceps delivery in R.O.A. position was accomplished after a deep left episiotomy. A live baby was delivered.

On the patient's first prenatal examination the cervix appeared bluish, without endocervicitis or erosion. There was a small, shallow ulcer, 3 to 4 mm. in diameter, in the anterior vaginal wall, but smears revealed no tuberculosis. This was promptly cleared up, so that I hardly think it had anything to do with the later stenosis.

though no dilatation had occurred. At the end of five hours effacement was two-thirds complete, but still no dilatation could be made out, and the opening in the external os could not be located digitally. Examination by speculum revealed a pin-point opening through which the finger was readily passed. Almost as soon as the canal had been entered, two fingers' dilatation occurred. Thereafter labor progressed normally and delivery of a healthy female child, weighing 7 pounds 14 ounces, took place four hours later (nine and a half hours after the onset of labor). In this case artificial measures were employed before complete obliteration of the cervix had occurred but might not have been necessary had labor been allowed to progress without interference.

CASE 2.—Mrs. M., a white female, aged 37 years, para iii, gravida v, had menstruated for the last time May 31, 1938, and expected delivery March 6, 1939. The present pregnancy had been normal throughout, and pelvicocephalography revealed normal fetopelvic relations.

Her previous history was without incident, except for two spontaneous abortions which occurred between the first and fourth full-term pregnancies. Both previous labors had terminated spontaneously in full-term, healthy children.

Labor began March 1, 1939, at 11 A.M., with strong pains at fifteen-minute intervals. The position was L.O.A. Vaginal examination eleven and one-half hours later revealed the cervix flush with the vaginal wall; the cervix was completely effaced and the impression was that the fetal head was covered by a snugly fitting cap. The external os as such could not be identified, but careful digital examination finally revealed a dimple pointing toward the vaginal fossa. When the finger was gently pressed into this area, it immediately gave way and the canal was entered without difficulty. Although no attempt at manual dilatation was made, two fingers' dilatation occurred within fifteen minutes, and complete dilatation was present at the end of an hour, following which a live, healthy male child, weighing 6 pounds, was delivered almost precipitately.

CASE 3.—Mrs. L., a white female, aged 29 years, para i, gravida ii, had menstruated for the last time September 4, 1938, and expected delivery June 11, 1939. The pregnancy had been normal throughout, and pelvicocephalography revealed normal fetopelvic relations.

The patient's first pregnancy had terminated in a premature labor at six months nine years ago. She had had several superficial cauterizations of the cervix and one deep cauterization for persistent endocervicitis. Three months prior to the inception of the present pregnancy tubal insufflation had revealed patent ostia.

Labor began at 4 A.M. June 18, 1939. The position was L.O.A. The pains were strong and regular from the onset. Eight hours later examination revealed the head well down and deeply engaged. The cervix was completely obliterated and was flush with the vaginal wall; the external os could not be identified. At the end of sixteen hours pelvic examination revealed the same conditions except that there was considerable edema of the tissues which covered the fetal head and it was impossible to differentiate the cervical from the vaginal tissues. The external os could not be identified digitally or by speculum.

It was obvious that the chances of the patient securing a living child would be jeopardized by further attempts at vaginal delivery. The vaginal canal was thoroughly sprayed with 4 per cent mercurochrome solution, and low cesarean section was performed. A healthy female child, weighing 8 pounds 1 ounce, was delivered without difficulty. After the placenta had been removed, the external os was immediately identified and two fingers' dilatation was accomplished by gentle pressure, this procedure being carried out routinely at cesarean section, in order to facilitate drainage. The patient made an uneventful recovery.

SUMMARY

1. So-called conglutinatio orificii externi is an unusual, though by no means rare, cause of delayed labor.

Blumenthal⁷ (1907) noted that the leucocytosis was more marked after separation of the placenta than in the first stage and that the count lessened after rupture of the membranes.

In 1910 Horvath⁸ stated that the peak of the leucocytosis occurred three to seven hours after delivery.

Baer⁹ in 1916 studied 100 cases in which he took counts during labor and one daily thereafter for ten consecutive days. In primiparas the average count was 18,225 during labor, with 19,887 as the high point on the first post-partum day. Multiparas revealed 13,467 cells during labor, with a high of 15,062 on the first puerperal day. He found the count to be higher during obstructed labor and after rupture of the membranes. There was a gradual decrease to a normal count within seven to ten days. Jarcho,¹⁰ Fawcett,¹¹ Cabot,¹² and others reached similar conclusions.

Gibson¹³ in 1937 investigated the subject in 38 normal cases. She recorded findings at the end of pregnancy, the height of labor, several times during the first twenty-four hours following delivery, and daily for two weeks in the puerperium. She observed a slight rise at the end of pregnancy and a much greater rise at the end of labor, with the highest average in the "birth to two-hour" period. Counts ranging from 10,000 to 39,800 occurred during the first six hours after delivery in normal women. The same type of leucocytosis was observed in primiparas as in multiparas, but in the former it tended to be higher and to last longer.

MATERIAL

Fifty normal women were observed shortly following the onset of labor to the termination of the eight-day hospital puerperium. Twenty-five were primiparas and 25 were multiparas. Leucocyte counts were made at intervals of one to two hours shortly following the onset of labor until delivery. Counts were then made at delivery, before and after the use of oxytocics, and after the delivery of the placenta. The hemoglobin and erythrocyte counts were likewise observed in 10 patients, but as these factors remained constant regardless of the change in the leucocytes further observations were not made.

The standard technique of making a leucocyte count from blood obtained by capillary puncture of the ear or finger, as described in all texts, was followed.

Several cases of rapid labor, primary uterine inertia, secondary uterine inertia, and "obstructed" labor were also observed.

RESULTS

Twenty-one of the 50 normal patients were seen during the last weeks of pregnancy. In these patients the counts varied from 5,750 to 12,200. The average count was 8,054.

All patients were seen from one to four hours following the onset of the symptoms of labor. In the 21 patients who had been observed before labor began, the counts at this time varied from 7,600 to 12,850. In all cases there was a slight rise over the previous figure. The remainder of the 50 cases revealed similar counts, the average for this time of labor being 10,247.

As labor progressed the leucocytes gradually increased. When the cervical os became dilated 4 cm. and the average labor pain was occurring every five minutes and lasting thirty to seventy seconds, the leucocyte counts varied from 8,240 to 14,050, the average being 11,456.

When the dilatation of the cervix had increased to 8 cm., the counts varied between 10,450 and 15,620. The average count was 13,635.

At approximately the onset of the second stage of labor the average count was 15,150. At this time the leucocytes ranged from 11,120 to 23,650.

Many leucocyte counts were made before, during, and after uterine contractions during the first and second stages of labor. No appreciable difference was noted.

Rupture of the membranes in itself did not influence the count; that is, the general pattern of the leucocyte rise, as observed in all cases, continued regardless of the time of the rupture of the membranes. Cases of so-called dry labor (14 of the 50 cases) likewise did not show any difference from the normal.

DR. CARTER (closing).—With regard to manual dilatation of the cervix at the time of cesarean section, I do not attempt to put a finger through the cervix in those patients who have been in labor, but I do in all patients in whom the section is elective. The reported section was comparable to an elective one, since there was no opening in the cervix and marked edema masked the structures.

Some years ago when I served as House Surgeon in the New York Lying-in Hospital, under the late Dr. Asa B. Davis, I assisted Dr. Davis in performing a cesarean section in which the cervix was left undisturbed. In this patient there was an absence of drainage through the vagina. On the third day she developed a temperature of 105°. I made a vaginal examination and found a dimple in the external os, through which I inserted my finger. Immediately there occurred a 2 cm. dilatation with a drainage of about 2 tablespoonsful of pus. The patient then ran a normal convalescence.

The same thing occurred in one of my patients at the Baptist Hospital in New Orleans, in whom the cervix failed to dilate after cesarean section. Vaginal examination disclosed a closed cervix through which the finger was inserted, resulting in evacuation of pus. The convalescence of this patient was also normal thereafter.

THE LEUCOCYTE COUNT IN LABOR*

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THE leucocyte count is a valuable laboratory procedure. It is a definite aid to the diagnosis, prognosis, and management of many disease processes. Its adaptation to obstetrics has largely been in the field of the associated medical and surgical complications. The occurrence of a leucocytosis during labor has been known since the observations of Moleschatt¹ in 1854 and Reider² in 1892. Although many individuals have studied the problem, the detailed relationship of the leucocyte rise to the clinical course of labor has not been determined. The following observations are reported in order to establish a "norm" because of the clinical significance the count might have when considering complicated cases.

In 1898 Hibbard and White³ noted that during labor the leucocyte count rose to 15,000 in primipara and 11,700 in multipara. This leucocytosis diminishes rapidly during the puerperium, with a slight elevation on the sixth day and a normal count thereafter.

In 1902 Habl⁴ studied 36 cases in the last months of pregnancy, during labor, and the first week post partum. He stated that there is a slight increase in the leucocyte count in the last few days of pregnancy, followed by a marked leucocytosis at the beginning of labor. This diminishes rapidly and is normal by the end of the first week post partum. The rise is in the polymorphonuclear cells.

Carton⁵ in 1903 found that a polymorphonuclear leucocytosis occurs during the last month of pregnancy, increases during labor, and is normal shortly afterwards. He found that the rise is more marked when the child is born dead or macerated, or when twins are present.

Given⁶ (1906) reported the average count to be 10,500 before labor, 16,000 twenty-four hours afterwards, and 7,000 by the twelfth day.

*Presented before the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 10, 1940.

Following delivery, counts were taken before, during, and at various intervals after the routine use of pituitrin and ergot. No change was noted.

The majority of women were also examined during the puerperium. The leucocyte count gradually returned to normal by the seventh day. Nine patients had a count slightly higher than that noted at delivery on the first puerperal day.

Eleven cases of short labors (three to seven hours) were observed. Six were multiparas and five were primiparas. In all cases a slight increase in the leucocytes occurred shortly following the onset of labor, a gradual rise continued, and at delivery the count varied from 13,600 to 17,450, the average being 14,980.

Four cases of primary uterine inertia were studied, all in primiparas. The labors varied from fifty-four to sixty-eight hours. They were all characterized by weak, infrequent, and irregular uterine contractions during the first stage of labor. Progress was slow until a cervical dilatation of 5 to 7 cm. was reached, when the labor pains increased so that delivery followed shortly. Conservative therapeutic measures were used. The count rose slightly following the onset of labor. During the slow and prolonged first stage the count remained at this same level. After good uterine contractions occurred, the count slowly rose so that a normal pattern was then followed until delivery.

Seven cases of secondary uterine inertia were seen. In all cases the normal pattern of leucocytosis was observed until the uterine contractions became weak and ineffectual. The leucocyte count then remained at the level it had reached at this time. In two cases strong contractions recurred spontaneously, and in these the leucocytes resumed their normal march to a higher level.

Six cases of what might be termed obstructed labor were observed (persistent occiput posterior, 1; deep transverse arrest, 2; disproportion, 3). The leucocyte count followed the normal pattern, except that the rise was higher in all cases.

DISCUSSION

Before one can assume that the pattern of leucocytosis is definite for labor, the changes must be compared with the leucocyte count in the normal nonpregnant individual.

The normal count of man is stated to be from 5,000 to 10,000, with 7,500 as the average count. Supposedly there is a physiologic leucocytosis following digestion and exercise, and the count is said to vary at different times of the day. These latter facts have lately been open to question. Smith and McDowell,¹⁴ Kenyon and Macy,¹⁵ and Ponder¹⁶ all noted that the white blood cell count is relatively stable throughout the day. Slight variations do occur, and an increase in the count in the afternoon is an inconsistent though fairly frequent phenomena. These changes do not appear to be due to an increase in new cells but to a redistribution of old ones. Each individual shows a slight curve of daily rhythm that is not modified by digestion, mild fatigue, moderate exercise, or menstruation.

The results reported show that a physiologic leucocytosis occurs during normal labor. It is also apparent that a definite pattern of leucocytosis is present. The onset of labor causes a slight increase in the leucocyte count. Following this, the leucocyte rise appears to be definitely related to the uterine contractions. Although the individual contraction does not influence the count, the sum total of many uterine contractions does. This is well exemplified by the course of the leucocyte count during normal labor, as compared to that in the uterine inertia series.

One cannot observe these changes without wondering what the cause may be. Previous workers have shown that the rise is only in the

Primiparas were observed every fifteen to twenty minutes during the second stage of labor. The leucocytosis continued, but in a more rapid fashion. The second stage of labor averaged two hours and eight minutes in these cases. The average count at the time of delivery was 22,250, with counts ranging from 14,760 to 27,640.

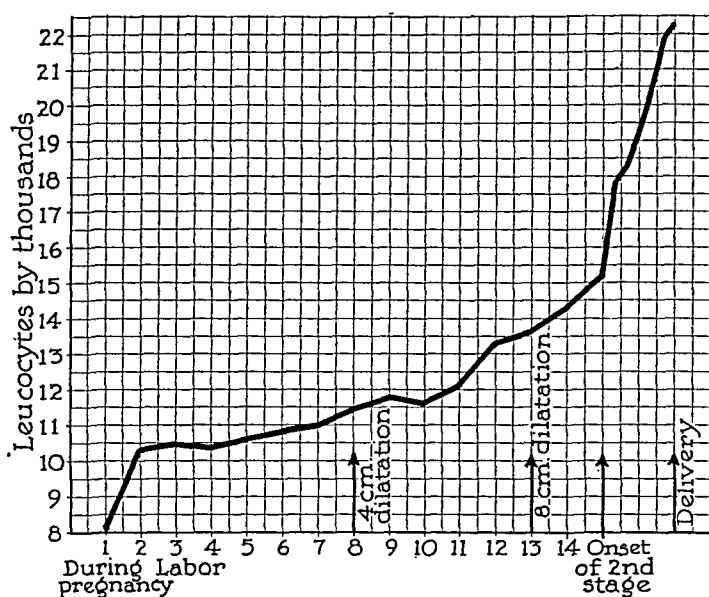


Fig. 1.—The leucocyte count in labor in primiparas.

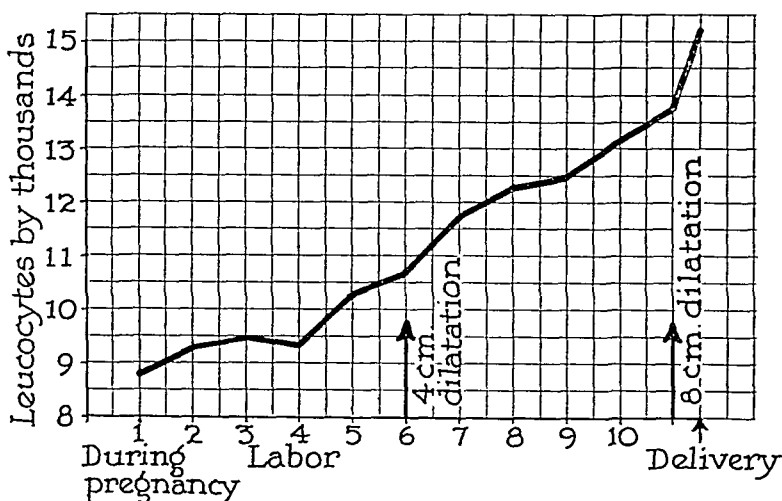


Fig. 2.—The leucocyte count in labor in multiparas.

This leucocytosis was also observed in multiparas. Counts taken near the end of pregnancy and shortly following the onset of labor revealed changes as reported above. As labor progressed, the leucocytosis continued. The counts gradually rose to $13,75 \pm$ (11,980 to 14,640) when 6 to 8 cm. cervical dilatation had been reached. Because the progress was usually rapid after this stage of labor had been reached, counts were then usually taken just before, during, and after delivery. The count at the time of delivery varied from 13,250 to 16,880, the average being 15,270.

The third stage of normal labor did not affect the leucocyte count.

blood stream. Another fact is the anoxemia which probably increases the count by opening up the blood sinuses. Anesthesia and analgesia of various kinds will produce anoxemia, thereby raising the leucocyte count. There is no mention in the paper of the type of anesthesia or analgesia used.

Most reports have shown that the leucocyte counts are higher after the termination of labor. That has been thought due to the fact that hemorrhage raises the leucocyte count. Yet the work done here shows no increase in the leucocyte count after the termination of labor. With this in mind, I would like to ask how much blood loss occurred in the patients reported here.

DR. WOLFF (closing).—As to the cause of the leucocyte rise we must admit that there are many possible factors. It has been shown that excessive exertion, such as walking up and down six flights of stairs or lifting a 1,400 pound weight, until exhausted, will raise the count, while moderate exercise has no effect. Adrenalin in large doses will also raise the count.

Regarding anoxemia, I observed 2 patients with compensated rheumatic heart disease, and in both the counts were exorbitant, 35,000 leucocytes being present at delivery.

In no case was analgesia used in the first stage, but drop ether was used for the final pains. The effect of analgesia or anesthesia upon the white blood cell count in these cases was, therefore, not important.

The higher counts noted after delivery by other workers have been found within two to six hours post partum. My first post-partum count was usually taken twelve to twenty-four hours after delivery. This may account for the variation.

There was no excessive hemorrhage in any case so that I do not believe that blood loss was a factor.

SOLID TERATOMA OF THE OVARY IN THE YOUNG GIRL*

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(*From the Division of Gynecology and Obstetrics, Henry Ford Hospital*)

THE solid teratoma of the ovary is a highly malignant growth when found in the adolescent or preadolescent girl. It occurs infrequently. The incidence of tumor is higher in the ovary than in any other organ of the growing girl. This tumor is more likely to be benign than malignant. The cystadenomas, the fibromas, and the cystic teratomas or dermoids are benign. The malignant tumors are either carcinoma, sarcoma, or the solid or combined cystic and solid teratoma. Among the malignant tumors, the solid teratoma occurs least frequently. The gross and microscopic appearance of solid teratomas rarely suggests malignancy, but subsequent data indicate that they are more malignant than carcinomas or sarcomas occurring in ovaries of girls.

An ovarian tumor is not suspected until it produces subjective symptoms. Steel¹ states that its presence may be made known in one or more of the following ways:

- (1) Increasing growth giving rise to abdominal deformity.
- (2) Constitutional disturbances, as precocious sexual changes.
- (3) Mechanical effects causing pressure on surrounding viscera.
- (4) Complications, e.g., torsion of the pedicle.

The latter complication is present in almost a third of the cases reported. Steel found 25 cases of cysts with twisted pedicle in which

*Read before the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

polymorphonuclear elements (primarily the neutrophiles) and that the cells morphologically represent mature and aged cells and not newly developed ones. Although many theories have been advanced, the present accepted one is that the count is the result of the muscular activity of the uterus.¹⁷ Whereas prolonged exercise does not affect the white blood cell count, severe activity can lead to a 60 to 100 per cent increase in the leucocytes.¹⁸ Since there has been no experimental work done here to decide this question, I can only state that the work of the contracting uterine muscle appears to stimulate the mobilizing of the polymorphonuclear leucocytes into the systemic circulation.

SUMMARY AND CONCLUSIONS

1. The leucocytosis of labor follows a constant definite pattern.
2. Normal values of the leucocyte count during the course of labor are established.
3. This pattern of leucocytosis is characteristic of both primiparas and multiparas, except for the higher numerical values during the longer second stage of labor of the former.
4. Comparison of the pattern in normal and abnormal cases shows the relationship of the leucocytosis to the uterine contractions.

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30 N. MICHIGAN AVENUE

DISCUSSION

DR. JOHN I. BREWER, CHICAGO, ILL.—The most interesting part of this paper to me is the demonstration that with uterine inertia, or when the uterine contractions are reduced in intensity, the white blood cell count does not increase; if the uterine contractions become more severe, the white blood cell count begins to rise. On this basis it has been concluded that the rise in the leucocyte count is the result of uterine contraction.

It seems, however, that there have been some factors that have been overlooked. With the increase in intensity of uterine contractions excessive exertion occurs and that alone will increase the leucocyte count. Another factor is the pain which itself will increase the leucocyte count to as high as 20,000. There is also an increase in adrenalin output which will increase the leucocyte count presumably by contraction of the spleen with extrusion of the leucocytes into the

very much caseation. There is no epithelioid cell reaction about these areas of caseation, nor are there any giant cells or other evidence to suggest tuberculosis, but some of these areas of degeneration are very extensive and are made up of light, homogeneous, pink-staining material in which we find pyknotic dead nuclei. There are other areas here in which the tissue seems to be loose, myxomatous, embryonic type of connective tissue, and in some places this contains areas of hemorrhage. A portion of the tissue present is covered by typical epithelium representing skin in which a cornified outer layer is present. There are other areas found which suggest endometrial tissue showing a stroma very much like endometrial stroma, loose in type, with cells somewhat like endometrial cells; this stroma shows the presence of glands which resemble to some extent endometrial glands. Some of the glandular elements in the sections show a few mitotic figures, but the cells are usually somewhat uniform in size and shape, and there is nothing at the present time which would suggest carcinoma developing within the tumor.



Fig. 1.

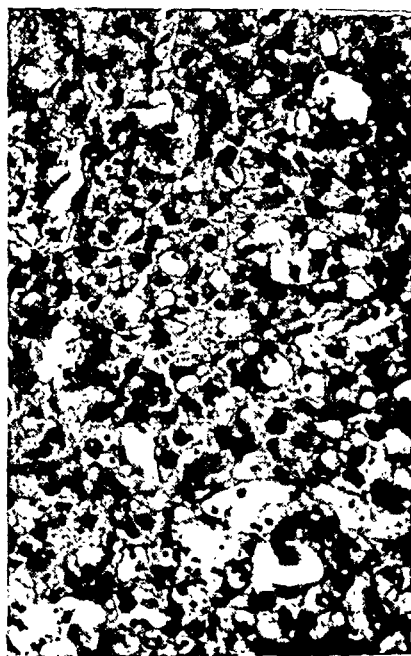


Fig. 2.

Fig. 1.—Photomicrograph, medium power, from Case 1, showing primary ovarian teratoma with areas of cartilage and epithelial lined spaces.

Fig. 2.—Photomicrograph, medium power, from Case 1, showing recurrent anaplastic tumor at time of second operation.

After remaining well for three months, the girl developed recurring attacks of lower abdominal pain. She did not see a physician until eight months later, when she was readmitted to the hospital because of these attacks. A suggestive or indefinite mass was palpable at the brim of the pelvis in the lower abdomen, and on rectal examination a definite mass could be distinguished. A second operation was delayed for three weeks because of clinical findings in the chest suggestive of tuberculosis. X-rays confirmed the diagnosis. During this time the mass rapidly filled the pelvis and lower abdomen. The abdomen was opened a second time on Dec. 2, 1933. The lower abdomen and pelvis were filled with a soft friable tumor, which was not encapsulated and which exuded from the incision. This tumor seemed to arise from the stump of the uteroovarian ligament on the right side. The left ovary was normal.

The parietal peritoneum of the anterior pelvis and abdomen was not involved. The liver and upper abdomen were normal. The mesenteric lymph glands were enlarged.

appendicitis was the preoperative diagnosis. This is logical inasmuch as both twisted pedicle cysts and appendicitis are associated with nausea, vomiting, lower abdominal pain, and with or without the presence of an abdominal mass. This error in differential diagnosis is not serious. Both conditions make surgical intervention imperative.

The preoperative differentiation between a benign or malignant tumor is not probable. It is important to know what to do if a solid tumor of the ovary is encountered. Solid tumors are usually pedunculated and are well encapsulated. If any adhesions are present, they are usually of recent origin. Gross evidence of extension or metastasis is lacking. The appearance of these tumors belies their true nature. It is to emphasize this point and to offer suggestions for treatment, that 2 cases are here reported.

CASE REPORTS

CASE 1.—K. S., aged 8 years, was admitted to the Henry Ford Hospital on March 7, 1933. She had been ill three weeks with abdominal cramps associated with nausea and vomiting. The family physician had made a diagnosis of intussusception.

On admission her temperature was 99.6° F.; pulse rate, 108; respirations, 22. She appeared ill. Examination of her nose, throat, and chest was negative. A swelling in the right lower quadrant was evident. A large, firm, tender tumor mass was palpated. Rectal examination was negative. The white blood cell count was 14,700, with 84 per cent polymorphonuclear leucocytes. Appendiceal abscess was diagnosed by the surgeon and consultant. On opening the abdomen a nodular tumor, measuring 9 by 13 by 6 cm., was found, involving the right ovary. The short pedicle had become twisted. There were no adhesions about the tumor. A large amount of bloody fluid was free in the abdomen, and there was no evidence of extension or metastasis. The tumor was removed by clamping and ligating the pedicle.

The pathologic diagnosis following microscopic examination was teratoma of the ovary. The gross and microscopic description of the tumor, as given by Dr. A. O. Severance, is as follows:

Gross Pathology.—The specimen consists of large mass, originating in right ovary, measuring 9.5 by 13 by 6 cm., and nodular, the nodules being cystic. The outer surface shows gray yellow and blue mottling. The vessels on the surface are dilated. On section the cut surface presents tumor tissue with areas of yellow gray. A cyst cavity, 5 by 2 cm., is found in one pole. Hemorrhage is seen in some areas. Gray areas on closer inspection have a translucent appearance and suggest colloid in places. The cyst cavity contains brown fluid. The total mass weighs 434 Gm.

Microscopic.—Various sections taken through the ovarian tumor show similar appearance. The tumor appears to be composed of an embryonal type of tissue in which portions of all three germ layers are present. In places we see glandlike alveoli lined by columnar type of epithelium in which the epithelial cells resemble goblet cells, and the epithelium lining this gland is very much like that found in the alimentary canal or intestinal tract. Other glands are smaller and contain cells that are more columnar in shape with pinker cytoplasm and blue nuclei. Also found throughout the ovarian tumor are numerous blood vessels, large and small, lined by flattened endothelial cells. Again portions of the tumor show large areas of connective tissue. Here and there we find areas of hyaline cartilage in which the matrix is light bluish in color, the lacunae are clear, and the nuclei of the cartilage cells are dark blue in color. Another cystic area is seen in which the lining epithelium is of the cuboidal or low columnar type, and this cyst shows the epithelium projecting outward in the form of many small villous-like projections. Another area shows stratified squamous epithelium, not very thick but very much resembling that found in the skin. Also found in the sections are areas of necrosis resembling

also visible. In some areas miniatures of long bones are seen showing caps of cartilage with active osteogenesis and small marrow cavity. Stratified squamous epithelium, some areas of which contain sweat and sebaceous glands, are noted. Numerous irregular glandular structures, lined by low cuboidal and tall columnar

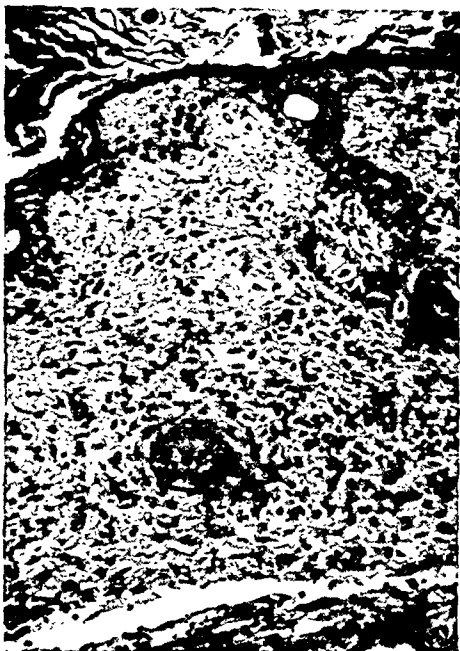


Fig. 3.

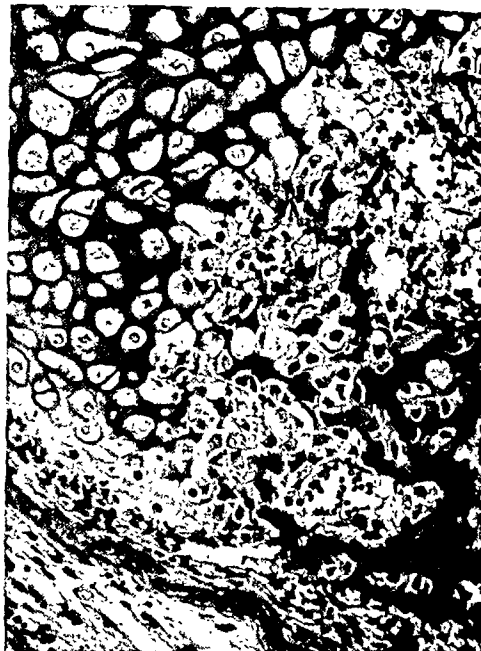


Fig. 4.

Fig. 3.—Photomicrograph, medium power, from Case 2, showing cyst lined by squamous epithelium and filled with epithelial debris. Cartilage is seen at bottom of field.

Fig. 4.—Photomicrograph, medium power, from Case 2, showing cartilage and bone from area resembling a femur.

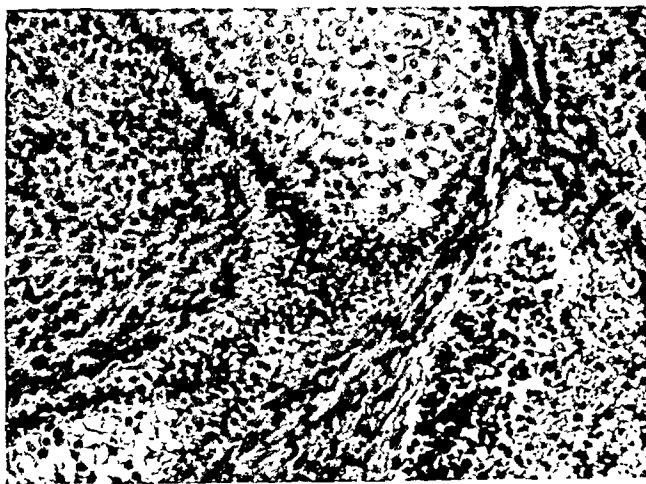


Fig. 5.—Photomicrograph, medium power, from Case 2, showing cellular poorly differentiated tissue in the recurrent tumor.

epithelium, are visible. Some of these structures resemble bronchiolar epithelium, and others resemble lung. In several areas structures resembling brain tissue and a few nerves are visible. There is no histologic evidence of malignant changes in the tumor examined.

The pathologic diagnosis was recurrent teratoma.

The gross and microscopic description of the tumor, as given by Dr. J. Lo-Cricchio, follows:

Gross Pathology.—The specimen consists of yellowish, fatty tumor tissue removed piecemeal. The largest piece is 6 cm. in its greatest diameter. The tumor has a semisolid papillomatous arrangement and a brainlike consistency. In a tube and a portion of the fundus of the uterus (uterine horn), we find tumor tissue adherent to the serosa throughout. This is a low papillomatous, grayish-red growth.

Microscopic.—Various sections from the tumor show a rather loose growth of cells with many capillaries and thin-walled vessels. These cells vary from spindle shape to polyhedral with clear cytoplasm containing numerous vacuoles, in some areas having slight resemblance to luteal cells, other areas appearing more like endothelium. The same type of cells are found throughout the tumor. There are some areas of necrosis and also hemorrhage with polymorphonuclear infiltration here and there. As to the cells themselves, they have either rounded or oval nuclei, which are hyperchromatic with red staining nucleoli and have coarse chromatin granules distributed throughout. There is slight variation in the size of the nuclei. Mitotic figures are fairly frequent. The outlines of the cells are not readily made out. In some areas, however, we observe cells which are rounded or polyhedral and have clear vacuoles in the cytoplasm; fat stains show the presence of lipid droplets in some of these vacuoles, but comparison of the H. & E. stain with fat stain shows that not all of these vacuoles are fat, since the tumor is much more vacuolated than the fat globules and the fat stain indicate. The cytoplasm, besides being vacuolated, shows fine pink granules. Occasionally we find small trabeculae of adult connective tissue. These are thin and insignificant, the bulk of the tissue being made up of this atypical cell whose origin is somewhat doubtful."

The girl was given a full course of deep x-ray therapy immediately. Within two weeks following the operation a definite recurrence of the tumor could be palpated in the lower abdomen. This tumor continued to grow rapidly until the child died on Jan. 23, 1934, less than one year after the first symptoms were noted.

CASE 2.—H. K., 14 years of age, was admitted to the hospital on Jan. 18, 1937, complaining of mild intermittent pain of two weeks' duration in the lower part of the abdomen. She had also noticed a swelling in the left lower portion of the abdomen. Her history was otherwise negative. The menarche was not yet established.

On admission her temperature was 102.4° F.; pulse rate, 108, respirations, 24. She was undernourished. Examination of the head, neck, and chest was negative except for some evidence of rachitis. Examination of the upper abdomen was negative. An irregular, firm, fixed tumor filled the lower half of the abdomen; this was not tender. On rectal examination the uterus was found to be displaced upward and to the right. The lower border of the tumor was palpable. At operation a tumor filling the lower abdomen and pelvis was found. This neoplasm was solid with cystic areas scattered over and through it. Small degenerated areas were bleeding. The tumor arose in the left ovary. The left infundibulopelvic ligament was edematous but not infiltrated. There was no gross evidence of extension. The tumor was excised with a wide margin. The tube was removed and the cornu of the uterus was widely resected. Her convalescence was uneventful.

The pathologic report following microscopic examination was teratoma of the ovary. The gross and microscopic description, as given by Dr. C. A. Payne, is as follows:

Gross Pathology.—The specimen consists of an irregular mass with a smooth fibrous capsule, weighing 950 Gm. The whole mass is soft and nodular. On section the parenchyma shows numerous grayish-yellow masses of tissue which represent degenerating cysts. Bits of bone are palpable throughout the tissue. Many varieties of tissue are seen. There is some hair.

Microscopic.—Section through the ovarian tumor shows a very bizarre structure containing elements from all three germ layers. Throughout the structure considerable amount of embryonal connective tissue is noted. Islands of cartilage are

Downes⁷ (1921) collected 21 cases of ovarian tumor occurring since 1904. All cases were under ten years of age. None of these tumors were classified as solid teratomas.

Well⁸ reported 60 cases up to 1904 but did not classify any of them as teratomas.

Harris⁹ reported a very interesting case in 1917. A subsequent report was published in 1925, ten years after the original operation. In the 1917 report he listed 21 cases of solid or cystic and solid ovarian teratomas which he found in the world literature. Twelve of these were of the solid type. In 1916 Seyforth⁹ assembled 171 ovarian tumors occurring in children under 15, of which only 23 were classified as teratoma. Luftspranger⁹ reported 4 cases in 1916. Probable duplication in the report prevents an accurate estimation of the incidence of these tumors. Loeb and Levy⁵ (1932) estimated that there had been about 50 cases reported. This figure is as nearly correct as one can estimate today.

The survival rate reported is low. The case reported by Frank³ survived and was well for two and one-half years after operation. May and Butsch⁴ did not see their case at the time of the primary growth, but saw it after a recurrence had taken place. Presumably this case did not survive. Of the 3 cases reported by Lanman,⁶ two died and one survived. Harris's⁹ case was alive and well ten years later. Of the 12 solid teratomas listed by Harris, 8 are known to be dead, one was alive and well for seven years, while 3 cases were reported too soon to be certain of their survival.

In Seyforth's⁹ series 20 were operated upon; 11 died within six months, and 4 had gone one year or longer without recurrence of the tumor.

In summarizing the foregoing data, we have a total of 32 cases, including the 2 in this report, in which we know the outcome. Twenty-one, or 65 per cent, of these cases are known dead, while the other 35 per cent have survived from one to ten years. Any special condition which carries a mortality rate of 65 per cent is indeed serious. The treatment needs careful consideration.

In the review of the literature it was noted that tumors were practically always pedunculated and the surgical treatment carried out was simple excision of the pedunculated tumor or adnexa on that side. The high rate of recurrence of tumor and death indicates that a more extensive surgical procedure is indicated. These tumors are usually well encapsulated. There is ordinarily a well-formed pedicle; seldom is there any more than very fine adhesions to the surrounding organs. The findings of extension or gross metastasis is rare at the time of the first operation. To all appearances when the abdomen is first opened the operator is dealing with a benign tumor, or at least one of very low malignancy. These observations, added to the fact that the patient is young, make it very difficult to proceed with radical surgery.

The pedunculated tumor recurs at the site of the original lesion. Later it spreads from this area by extension as well as metastasis. However, metastasis seems to be a late manifestation. This observation further emphasizes the need for wider excision at the time of removal of the primary growth.

The effect of roentgen-ray therapy upon this type of tumor is debatable. The only use of this form of treatment mentioned in the literature was by Frank.³ He followed the surgical removal of the tumor in his patient with deep therapy. One and one-half years later the patient showed no evidence of recurrence of the growth.

Frank³ compared his result with that obtained in a case seen in consultation. This patient also had a well encapsulated solid teratoma of the ovary which was

Inasmuch as the patient was feeling well she would not return for postoperative examination. She was finally persuaded to come to the office six months later. On abdominal examination a mass was palpated above the symphysis extending one-third of the distance to the umbilicus. The circumscribed tumor seemed movable and was not tender. There were no subjective symptoms.

A second operation was advised, but the patient did not come to the hospital until a month later. At this time the upper border of the tumor, as determined by abdominal palpation had extended one-half the distance to the umbilicus. At laparotomy on Sept. 8, 1937, a circumscribed solid and cystic tumor was found to have infiltrated and invaded the omentum and fundus of the uterus. There was also involvement of the sigmoid colon as well as many implants scattered over the pelvic peritoneum. Examination of the upper part of the abdomen was grossly negative. As much of the tumor as possible was removed. The pathologic diagnosis was recurrent teratoma of the ovary. The gross and microscopic description, as given by Dr. C. A. Payne, is as follows:

Gross Pathology.—The specimen consists of an irregular, lobulated, and cystic mass, weighing 476 Gm. The tumor appears to be circumscribed, but the surface reveals many small cysts filled with a serous and mucinous fluid. On section the mass contains innumerable small cysts, composed of a light gray soft tissue which is hyperemic and shows some hemorrhagic infiltration. This tissue is supported by strands of a more fibrous nature. In a few areas there is evidence of calcification.

Microscopic.—Section through the tissue received in many areas reveals many gland spaces, some of which are lined by columnar epithelium and others are lined by squamous type of epithelium. Many glands are markedly distended and show degenerated leucocytes as well as epithelial debris. The stroma of the tumor is composed of very embryonic connective tissue, many areas of which show a myxomatous type resembling the jelly of Wharton. Many islands of embryonic cartilage are noted throughout. Masses of squamous epithelium, which show mild degree of differentiation, are also noted throughout the tumor. Some portions of the tumor are extensively necrotic and infiltrated by numerous red blood cells and polymorphonuclear leucocytes.

The patient was given a course of deep x-ray immediately, and again ten weeks later. Shortly before the second series of x-ray treatments was given, ascites appeared. No masses were palpated in the abdomen until after the second course of treatments. The abdomen then rapidly filled with recurrent tumor tissue, and the girl died in February, 1938, fourteen months after she experienced the first subjective symptoms.

DISCUSSION

In discussing the treatment of solid teratoma of the ovary, one should be familiar with its frequency and degree of malignancy. There are numerous papers in more recent literature concerning ovarian neoplasms of the young girl. These papers deal mainly with ovarian cysts, primary malignancies, or cystic teratomas. Many reports are not complete enough to allow one to judge whether the tumor is a solid or a cystic teratoma.

Witzberger and Agerty² collected 63 cases of ovarian neoplasms occurring in girls under 11 years of age. They reviewed the world literature between the years 1921 and 1937. Only one case cited was a solid teratoma. This case was reported in 1932 by Frank³ and will be referred to again. An additional case was reported by Mayo and Butsch⁴ in 1938.

Loeb and Levy⁵ (1932) reviewed the literature on ovarian neoplasms occurring in the same age group. There was no reduplication of cases. From 1921 to 1931, they found 33 cases among which 3 can definitely be classified as solid teratoma of the ovary. One case was classified as a teratochorioepithelioma; the other 2 cases were reported from the Children's Hospital in Boston by Lanman.⁶ In 1929 Lanman reviewed the admissions to the surgical service of the Children's Hospital in Boston during the preceding ten years. Of 12,260 children under 12 years of age who were admitted there were 5 with ovarian tumors. Three of these had solid teratomas; the fourth, a cystic teratoma or dermoid; and the fifth, a solid carcinoma.

A STUDY OF 107 CASES OF UTERINE BLEEDING WITH ENDOMETRIAL BIOPSIES*

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IN UNDERTAKING this study there were a number of factors to be considered, and to leave out the rather statistical or prosaic phases of such discussion, the following are briefly some of our findings in work extending over a period of about three years.

These biopsies were obtained in the biopsy clinic of the Out-Patient Department of Gynecology and Obstetrics, Hillman Hospital, Birmingham, Alabama. They were taken without giving the patient an anesthetic. We attempted to get four specimens from each woman at weekly intervals to study the different phases of the endometrium. This study was done on patients who had uterine bleeding or menstrual irregularities, and there were a great many other patients who were seen but their attendance was not regular and they are not included in this group.

Very few of these patients came in with any suspicion of having had an abortion or suspecting retained placental tissue, but we were surprised to find 15 patients, or 14 per cent of the 107 patients, showing placental tissue which accounted for the bleeding. This is a much higher percentage than we would have believed unless the endometrial biopsies were taken to prove it.

Of the different phases of the endometrium, we found there were 95 of the 267 specimens in the proliferative stage. The pathologist found 87 in the early proliferative and 8 in the late proliferative phase. In this group 2 were found to be glandular hyperplasia and 3 to be glandular dysplasia and 2 polypoid hyperplasia.

There were one case of cystic glandular dysplasia reported and 23 of atrophic endometrium present.

This research was done, not primarily with the idea of malignancy, for where such is suspected we advise dilatation and complete curettage, but we were interested to find that there were three cases, or 2.8 per cent, of the 107 cases. This was striking, and at the same time, stimulating to us to make a more careful study of all uterine bleeders.

We noted that a great percentage of these patients who had irregular menstruation or bleeding were relieved after the 4 biopsies were taken without any further medication. So certainly, there are a large number of bleeders who have this condition present due to endocrine imbalance or endometrial disturbance and the comparatively small amount of tissue which was removed with the biopsy curette was sufficient for them to

*An abridgment of paper presented at the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Indiana, October 12, 1940.

removed surgically. She was not treated with x-ray. The tumor recurred and the patient died. Frank believes that the x-ray treatments received by his patient were the deciding factor.

Both cases that I have reported received roentgen therapy. In both instances there was clinical evidence of recurrence of the tumor before the x-ray was given. In the first case, the recurrence was proved to be extensive by the laparotomy which had been performed a short time previously. The girl received one series of treatments anteriorly and posteriorly through ports covering the entire pelvis and lower abdomen. The rate of growth of the tumor was apparently not slowed and by the time the second series of treatments could have been started, the extent of the growth and the condition of the patient prevented it.

In the second case, recurrence appeared before roentgen therapy was given. The girl was given as much x-ray as she could tolerate. The first series was given immediately after the second operation; the second series ten weeks later. Ascites developed two months after the first series of x-ray. No masses were palpable in the abdomen at that time. However, shortly after the second series of treatments were given, a mass was present in the lower abdomen. The ascites continued to develop more rapidly as the lesion progressed.

We have no evidence in either case reported that the x-ray had any effect upon the tumor growth. For this reason, we question the efficacy of deep therapy in this form of growth. We agree with Frank³ that these cases should be given x-ray in therapeutic amounts immediately after the primary operation. How effective x-ray will be in preventing a recurrence we do not know, but we do not believe it is beneficial after recurrences are present. We believe that more emphasis should be placed upon a wider excision of the original growth. This means removal of all the pelvic viscera as widely as the operator's experience allows him to dissect. The operation should then be followed by x-ray in the amount compatible with the patient's age and size. Girls with teratoma should be treated in a manner similar to adult women with carcinoma of the ovary.

SUMMARY

1. The solid teratoma when found in the ovary of the young girl is extremely malignant.
2. The literature is briefly reviewed and 2 cases of teratoma are reported.
3. The cure of this tumor depends upon complete surgical removal.
4. Our experience with the roentgen ray has not been encouraging.
5. These tumors should be treated similar to other malignant tumors occurring in the ovary.

I am greatly indebted to Dr. J. P. Pratt for his suggestions in the preparation of this manuscript, and to Dr. F. W. Hartman for the preparation and description of the photomicrographs.

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In this group of women there were 70 gravidas and 37 nongravidas.

One point of interest was the number who had positive Wassermann reactions: there were only 7.1 per cent of these including both colored and white. It is not our opinion that the positive Wassermann reactions had a very great deal of bearing as a causative factor in the bleeding of these patients. Of course, there might have been some who had constitutional upsets that would have caused bleeding such as you find with other types of anemia.

All of these specimens were obtained by the use of the suction curette; we preferred this to the ordinary bite curette, for we are able to obtain more tissue and go over a larger endometrial area than we probably would with an ordinary bite curette.

It has been instructive to observe some of these cases over a period of more than three years which has enabled us to keep up with their menstrual history and have noticed that without treatment, other than the biopsy, they are corrected and would go for a number of months without any other menstrual disturbance.

Some of these cases have shown decided changes in the amount of endometrial tissue after the administration of one of the gonadotropic substances. So, certainly, there is a place for their use in these bleeding cases if a proper diagnosis has been reached. But it is quite essential to study the endometrial tissue before administering the gonadotropes.

There has been a marked decrease in the number of bleeding patients admitted to the Hillman Hospital for dilatation and curettage since this biopsy clinic has been going; for the majority of them we are able to diagnose and give such treatment in the clinic so they do not have to be admitted. It is well to have some means of a clearing house for these patients before admission. Naturally, we have a large number in a charitable institution, such as this. The daily average for the hospital for 1939 was 337 patients with a bed capacity of 450.

Of the endometrial biopsies there were 23 specimens which showed atrophic endometrii, which indicates that a number bleed even though the endometrium is of the atrophic type.

The hope for correct treatment lies in the accurate diagnoses, and much can be done in the study of uterine bleeders of the nonmalignant type. When we are able to do assays more generally to determine as to whether there is an excess or deficient amount of estrogenic or gonadotropic substance in the system, we shall be able to know more how to prescribe for our patients' needs.

While we are going through this process of investigation, we should be less prone to radical surgery unless there is pathology such as malignancy, fibroids or other trouble that cannot be corrected with medical treatment. If we will properly discuss the prognosis with these patients, letting them know that these are tedious conditions to deal with and require time, not only for several months but a year or so, they will be more cooperative and help us a great deal.

I feel that in all cases of uterine bleeding basal metabolism tests should be done, because there are many women who have thyroid,

TABLE I. ONE HUNDRED SEVEN CASES, TOTAL BIOPSIES 267

	PROLIFERATIVE PHASE, LATE AND EARLY	SECRETORY PHASE, LATE AND EARLY	HYPERPLASIA OF ENDOMETRIUM	GLANDULAR HYPER- PLASIA	POLYPOID HYPER- PLASIA	ENDOMETRIAL GLANDU- LAR DYSPLASIA	CYSTIC GLANDULAR DYSPLASIA	PLACENTAL TISSUE	MALIGNANT ADENOMA	ATROPHIC ENDOMETRIUM
Number of biopsies	95	95	28	2	2	3	1	15	3	23
Per cent of total biopsies	35.5	35.5	10.4	0.74	0.74	1.08	0.3	5.5*	1.08†	8.6

*This is the per cent of total 267 biopsies taken. (The per cent of placental tissue found in 107 cases was 14 per cent.)

†This is the per cent of total 267 biopsies taken. (The per cent of malignancies in 107 cases was 2.8 per cent.)

become regular. There are a great many who have endometrial tissue at different stages of development at the same time and to have this tissue removed in a sense regulates or starts the stages of development equally.

We felt that one of the best times to obtain these specimens, as far as giving information is concerned, is about the time menstruation is over as we would come nearer getting the basal cells for study, but we obtained them at weekly intervals regardless of the stage of the menstrual cycle.

The average age of this number of patients was thirty-eight years, the youngest fourteen and the oldest sixty-nine. One of the older patients who had continued bleeding after the biopsies were made with report of endometrial hyperplasia, was admitted to the hospital and a laparotomy was done, finding the uterus was rather normal in size, and ovaries very slightly enlarged, but with history of bleeding, hysterectomy was done, also bilateral oophorectomy. On microscopic examination patient was found with granulosa cell tumor of the ovary.

The average number of biopsies in this series of study was 2.4 per patient with the total ranging from 1 to 24 biopsies to each patient.

In the past we have been prone to overlook the ovaries of uterine bleeders too frequently. Cystic ovaries or other pathology, such as granulosa cell tumor cases of the ovary, is often the controlling factor, in fact the whole cause.

With the study being made on the endometrial tissue if we could do a laparotomy at the same time with resection of these presumably simple cysts in the ovary, as well as some of the solid tumors of the ovary, this would prove of very great value.

In consideration of the race as to white and colored, there were 75 whites and 32 colored individuals in this series, which is interesting, for in our general gynecologic clinic we have a rather high percentage of colored patients and a great many of them have fibroids, so you see the incidence of bleeding with fibroid is less than the bleeding which occurs with the endocrine disturbances.

THE THERAPEUTIC VALUE OF TUBAL PATENCY TESTS IN STERILITY AND INFERTILITY*

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THE determination of tubal patency is accomplished by two well-established methods: the insufflation of gas and the injection of iodized oil. Transuterine tubal inflation was first performed by Rubin in 1920 as a means of testing tubal patency, and the use of iodized oil in visualizing the Fallopian tubes was first reported by Heuser in 1924, although previously (1914) Cary attempted hysterosalpingography using collargol as the radiopaque substance. From the use of these methods as exclusively diagnostic procedures, their therapeutic value soon became evident.

In 1932 Rubin collected 764 cases of pregnancy from the literature, all of which were attributed to the effects of insufflation. In his own series, 17.5 per cent of those patients who were insufflated for sterility became gravid. His results were particularly noteworthy in 570 cases in which were demonstrated some organic obstruction to tubal patency, such as adhesions or strictures. Of this group, 123, or 21.6 per cent, became pregnant. Rubin concludes that tubal insufflation has a definite therapeutic value in sterility. This is attested by the actual improvement in tubal patency and function during repeated insufflations and the pregnancy which follows shortly afterward. He condemns the use of lipiodol as dangerous, and limits its use to those cases where insufflation reveals the presence of closed tubes or high-grade obstructions. However, in 9 of his cases where gas insufflation revealed nonpatency, lipiodol succeeded in passing the fimbriated end. On the other hand, patency was demonstrated to gas but not to oil in 8 patients. The literature is replete with many other reports substantiating the therapeutic value of insufflation. Series of case studies have been reported by King (11.6 per cent), Chatillon (15.2 per cent), Bonnet (18.4 per cent), Violet (6 cases), and Mintz. The latter found that diathermy combined with insufflation exerted a curative effect upon some chronically diseased tubes, leading to restoration of patency and subsequent pregnancy. Of 44 cases, patency was re-established in 25, and in the latter 9 pregnancies occurred. Stein and Leventhal, in analyzing 300 sterile couples, reported 26.3 per cent pregnancies out of 57 infertile couples treated by perturbation alone, the pregnancies occurring immediately to more than one year after the test.

The value of oil instillation as a therapeutic measure and its superiority to gas insufflation is supported by many authors, especially the French, who were the first to recognize the therapeutic effect on sterility of iodized oil used in hysterosalpingography.

In 1936 Francillon-Lobre and Dalsace reviewed the results obtained with hysterosalpingography in 585 cases of sterility collected over ten years. Of this number, 434 showed patency to one or both tubes, and 89, or 20.5 per cent, conceived. In 6 cases pregnancy supervened even though the tubes were impermeable to oil. The

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either hypo or hyper conditions, in whom, if properly diagnosed and treated, the bleeding can be corrected.

The study of these bleeders as to decades is shown in Table II.

The ages of the patients with malignant conditions were 26, 51, and 59 years. Malignancy is no respecter of persons or age, so we should not let a patient who is bleeding go without a thorough examination, regardless of whether she is of the younger or older group.

TABLE II

1	10-20 years	7
2	20-30 years	32
3	30-40 years	39
4	40-50 years	17
5	50-60 years	10
6	60-70 years	2

We are very much gratified in the findings of these patients whose condition was in the earlier stages, and if we are more diligent in doing biopsies early, we will find more of these malignancies at a stage in which something can be done for them.

SUMMARY AND CONCLUSIONS

1. An examination of the endometrial tissue is of great importance, as it closely reflects the functional activity of the ovaries in most cases of abnormal bleeding.

2. A diagnosis of irregular menstruation as a pathologic condition should always be made with a great deal of hesitancy, owing to the variation of the cycle of normal individuals.

3. The menstrual cycle is definitely under the control of the endocrine system. The most fundamental glands bearing relation to this function are the anterior hypophysis, the ovaries, and the thyroid.

4. In this study of 107 cases over a period of three years, the average age was 38, the youngest 14 and the oldest 69.

5. The average number of biopsies was 2.4, ranging from 1 to 24 to each patient.

6. The number of positive Wassermann reactions was 7.1 per cent, including both whites and colored. In our opinion this was no factor in the cause of bleeding.

7. There were 75 white and 32 colored patients.

8. The incidence of malignancies found in this group unsuspected was 3, or 2.8 per cent, of the 107 cases, ages of patients being 26, 51, and 59 years.

9. There were in this group 15, or 14 per cent, who had retained placental tissue.

I wish to thank Dr. Harold Imerman and Dr. Reuben Harris, Residents on Gynecology and Obstetrics, Hillman Hospital, also Dr. J. W. MacQueen, Director of the Hospital, Dr. George S. Graham and Dr. L. C. Posey from the Department of Pathology, and other members of the Staff who referred cases for study.

The tubal patency test, using carbon dioxide or lipiodol or both, was performed on 165 patients. Eliminating those patients from this group in which male deficiencies and definite glandular dyscrasias were factors, there remained 133 patients in whom the importance of tubal insufflation or oil instillation as a therapeutic measure could be evaluated. Of these 133 patients, 114, or 85.7 per cent, demonstrated patency of one or both tubes to gas or oil, and of the latter, 51, or 45 per cent, became pregnant. Nineteen, or 14.3 per cent, demonstrated no patency, and only 3 of these, or 15.8 per cent, became pregnant. *Thus 54, or 40.8 per cent, of the entire group of 133 patients became gravid.* The average duration of marriage in the successful group was 3.8 years as compared with 5.2 years in the unsuccessful group, and the duration of sterility in the two groups was 1.7 years and 3.0 years, respectively (Table I).

TABLE I. ANALYSIS OF 133 PATIENTS IN WHOM THE THERAPEUTIC VALUE OF THE PATENCY TEST COULD BE ESTIMATED

	NO.	AGE (AVG.)	MARRIED (AVG.)	DURATION STERIL- ITY	PATENCY +	PATENCY -
Pregnancy	54 (40.6%)	27.7 yr.	3.8 yr.	1.7 yr.	51	3
No pregnancy	79 (59.4%)	31.2 yr.	5.2 yr.	3.0 yr.	63	16
Total	133				114 (85.7%)	19 (14.3%)

In 38, or 28.5 per cent, of the patients pregnancy occurred within two months of the patency test. Some other form of therapy which might have been responsible for a cure of sterility was employed on 10 patients in this group, 7 having had cervical cauterization for erosion and endocervicitis, and 3 thyroid therapy, even though the basal metabolic rates were within normal range. The cauterizations were done six months or more before the patency test. Generally accepted criteria by which the responsibility of insufflation may be estimated include pregnancy within two months and the absence of other therapeutic measures. Since 28 patients in our series met these requirements then *21.5 per cent of the patients on whom the tubal patency test was performed became pregnant, the pregnancy being attributed directly to the procedure.* Further support for the therapeutic value of the patency test in these cases is added by the fact that the average duration of sterility was 1.7 years and the average duration of marriage for the group was 3.8 years. The longest duration of marriage was thirteen years and the shortest was one year. The longest duration of sterility was nine years and the shortest was six months. Of the 28 successful patients who became pregnant within two months, and on whom no other form of therapy was used, 14, or 50 per cent, conceived immediately without an ensuing menstruation; 23, or 82 per cent, conceived within one month of the patency test. There were 6 patients in the successful group, or 15.8 per cent, who had some associated pathologic condition (Table II). One had fibroids, 2 had a third degree retroversion of the uterus, 2 had a history of previous febrile abortion, and 1 had a previous pelvic laparotomy. In one patient who had a previous septic abortion, no patency was demonstrated with either gas or oil, and in the other, gas did not pass through, but the oil entered the peritoneal cavity after twenty-four hours. In the 2 patients who exhibited third degree retroversion, the tubes were impervious to gas and demonstrated patency to oil only after twenty-four hours. The incidence in the group that failed was 44.3 per cent. Table III demonstrates the relationship of the patency test to pregnancy and associated pathology in the 133 cases. Of the 63 unsuccessful cases with positive patency, 27, or 42.5 per cent, had associated pathology. Thus the factor of associated pathologic conditions is an important one in influencing the therapeutic effect of insufflation and oil instillation. The associated pathologic conditions, encountered in the order of their frequency, included previous pelvic laparotomy, fibroids, previous febrile abortion,

authors conclude that if a sterile woman has one tube patent, she has one chance in five to become pregnant after hysterosalpingography. Robins and Shapira did uterotubography in 330 patients with sterility. In 133 of this group in whom one or both tubes were found or caused to be patent, 32 per cent became pregnant. Other authors who have reported cures of sterility following oil instillation are White (32.5 per cent), Beclere and Francois (18 per cent), Volk (25 per cent), Wilson (26.3 per cent), Brault and Tizon (26 per cent), and Schultze (25 per cent). Most of these declare that the risks associated with lipiodol are not greater than with carbon dioxide, and the therapeutic results are better with the former.

The method we used in the investigation of sterility is as follows: We thoroughly investigated the patient complaining of sterility for extrapelvic factors, such as foci of infection, chronic debilitating diseases, and glandular dyscrasias. If vestiges of recent pelvic inflammatory disease are not found and if the cervix displays no evidence of infection, the patient is instructed to report to the office on a date approximating the time of ovulation (figured in accordance with the cycle). She is also instructed to have normal coitus just before the office appointment. Material for a Huhner postcoital sperm test is obtained by aspirating some cervical mucus with an "asepto" syringe. The cervical mucus just within the external os is then removed following liquefaction with caroid powder; and after drying the external os cervix and vaginal vault with cotton pledgets, a 2 per cent aqueous solution of mercurochrome is applied topically. The direction of the cervical canal is determined with a sterile uterine sound, and the Stein self-retaining cannula is inserted. Carbon dioxide is insufflated transuterinely under low pressure, using the Rubin apparatus with manometric control. The tubes are declared impermeable to gas if no patency is demonstrated after three attempts up to 200 mm. Hg pressure. *We have noticed no ill effects or infections which could be attributed to the preliminary intercourse, and feel that this routine is probably a factor in the high percentage of pregnancies which followed insufflation in our series of cases.* If the tubes are not patent to gas, the patient is instructed to report for lipiodol instillation within the following day or two. This examination is carried out in the hospital x-ray department and serial roentgenograms are taken, including a twenty-four- or forty-eight-hour film if no patency is shown initially. If lipiodol instillation fails to reveal any tubal patency, it is repeated in two months. In cases of tubal closure, the x-ray demonstrates the site of obstruction and is invaluable in selecting cases suitable for surgical intervention. In a few cases in our series where tubal obstruction was encountered, one ampoule of surgical pituitrin was administered hypodermically with the instrument in situ in an attempt to overcome adhesive closure by increasing intracavitary pressure. In some instances the presence of intrapelvic pathology was questionable and pneumoroentgenography was performed using the combined method of Stein and Arens. In these cases pneumoperitoneum was always attempted by the transuterine route first and lipiodol was instilled unless contraindicated.

ANALYSIS OF CASES

Between January 1, 1930, and January 1, 1940 (ten years) 285 patients complaining of sterility or infertility were thoroughly investigated in our private practice. A critical analysis of these cases was undertaken in order to evaluate the importance of tubal insufflation and oil instillation as therapeutic measures. In the entire group of 285 patients, considering all etiologic factors and all types of treatment, conception occurred in 88, or 31 per cent. Not every patient who consulted us for sterility had a patency test performed. When an obvious cause was discovered at the initial examination, it was treated first. Thus, chronic endocervicitis with erosion or eversion was encountered in many instances, and its eradication by cautery was followed not infrequently by conception.

of associated pathology in the successes in this group adds further weight to the role of lipiodol in overcoming tubal dysfunction and obstruction. This was further illustrated in 3 of our successful cases where the tubes showed no patency to either gas or oil. One patient had a previous febrile abortion, and examination revealed a third-degree retroversion. Patency to gas failed on two occasions. Two oil instillations done four months apart failed to show "spill" after forty-eight hours. After the second instillation pregnancy occurred without an ensuing menstruation.

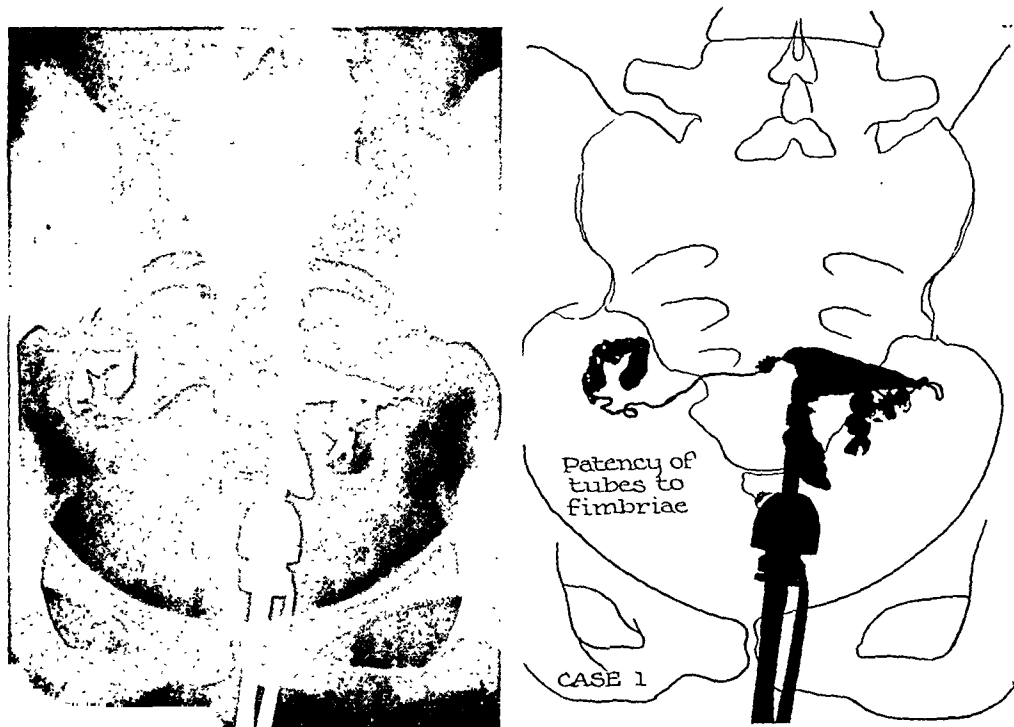


Fig. 1.—(Case 1.) Illustrating closure of tubes at the fimbriae. Previous gas insufflation negative.

The second case, with a third-degree retroversion, failed to show patency to oil on two occasions, and pregnancy followed within three months of the last test; and the third, after three negative results with oil, conceived over one year later. These cases demonstrate as prima facie evidence the curative role of lipiodol instillation in the treatment of sterility.

Other illustrative case reports include the following:

ILLUSTRATIVE CASES

One patient, C. H., who was married nine years and was sterile seven years had three previous positive patencies performed with carbon dioxide in the past six years. Instillation of lipiodol was followed within three months by pregnancy.

Mrs. T. B., was married thirteen years and sterile for nine years. The tubes were nonpatent to gas in three attempts to 200 mm. Hg pressure. Oil instillation the following day revealed the tubes patent to the fimbriated ends, and "spill" was noted after twenty-four hours. Pregnancy occurred without an ensuing menstruation.

Pregnancy occurred within two months in Mrs. J. P. who showed the same findings as Mrs. T. B., after a period of sterility of eight years.

Mrs. L. P., married 3 years, complained of sterility for one and one-half years. The Huhner and patency tests showed normal sperm, but no patency to gas. The following day, insufflation was again attempted and was found negative. Instillation

TABLE II. ANALYSIS OF PREGNANCIES WITHIN 2 MONTHS OF PATENCY TEST (38 PATIENTS)

	NO.	OTHER THERAPY*		NET RESULTS 133 CASES		AGE (AVG.)	MAR- RIED (AVG.)	STERILITY			ASSOCI- ATED PA- THOLOGY
		CAU- TERY	THY- ROID	NO.	%			DURA- TION	PRI- MARY	SEC- ONDARY	
Pregnancy stat.	17	3	0	14	10.5	29 yr.	4.0 yr.	1.6 yr.	12	5	4
Pregnancy in 1 month	12	2	1	9	17.3	28 yr.	4.0 yr.	1.7 yr.	11	1	1
Pregnancy in 2 months	9	2	2	5	---	26 yr.	3.3 yr.	1.8 yr.	7	2	1
Total	38	10		28	21.5	27.7	3.8 yr.	1.7 yr.	30	8	6 (15.8%)

*The average time by which cautery preceded insufflation in the 7 patients was 6 months.

The B.M.R. rate was normal in the 3 patients who received thyroid therapy.

TABLE III

ASSOCIATED PATHOLOGY IN PATIENTS TREATED BY PERTUBATION (133 CASES)*

PATENCY CO ₂ AND LIPI- DOL	SUCCESSFUL (PREGNANCY)		FAILURE (NO PREGNANCY)	
	TOTAL NO.	ASSOCIATED PATHOLOGY	TOTAL NO.	ASSOCIATED PATHOLOGY
CO ₂ +	22	5 or 22.7%	30	12 or 40.0%
CO ₂ + Oil +	15	2 or 13.3%	20	10 or 50.0%
CO ₂ + Oil -	1	0	5	3 or 60.0%
CO ₂ - Oil +	13	7 or 53.9%	7	2 or 28.7%
	3	3 or 100 %	7	6 or 85.7%
CO ₂ -	0	0	9	2 or 22.2%
Oil +	0	0	1	0
Total	54	17 or 31.4%	79	35 or 44.3%
Patency +	51	14 or 27.5%	63	27 or 42.5%
Patency -	3	3 or 100 %	16	8 or 50%

*In order of frequency: previous pelvic surgery, fibroids, previous febrile abortion, adnexitis, retroversion, ovarian cyst, previous ectopic pregnancy, previous puerperal sepsis.

adnexitis, retroversion, ovarian cyst, previous ectopic pregnancy, and previous puerperal sepsis. Even without any obvious palpatory findings, previous pelvic surgery and previous septic abortion were included, because with these conditions there may occur functional changes in the Fallopian tubes and indiscernible adhesions. It is to be noted that the incidence of associated pathology is greater in the series of failures than in the successes with the exception of 2 groups in the successful series; namely, where the tubes were nonpatent to gas but patent to oil, and where nonpatency was demonstrated with both agents. This demonstrates the value of the test in overcoming tubal obstruction.

A total of 42 per cent of all the patients in whom the tubes were patent to gas alone or gas plus oil became pregnant (37 of 87). A positive illustration of the therapeutic value of insufflation alone is demonstrated by one patient in our series, who conceived immediately after the Huhner and patency tests on two occasions three years apart. Preceding each test, there was a one-year period of infertility. In six instances where the tubes were patent to gas but nonpatent to oil, pregnancy occurred only once. Thirteen of 20 patients who demonstrated no patency to gas and who later evidenced patency to lipiodol became gravid; whereas none of 9 patients who were negative to gas and on whom there was no follow-up with oil conceived. This observation may be interpreted as evidence for the superiority of lipiodol instillation over insufflation in the cure of sterility. The high incidence

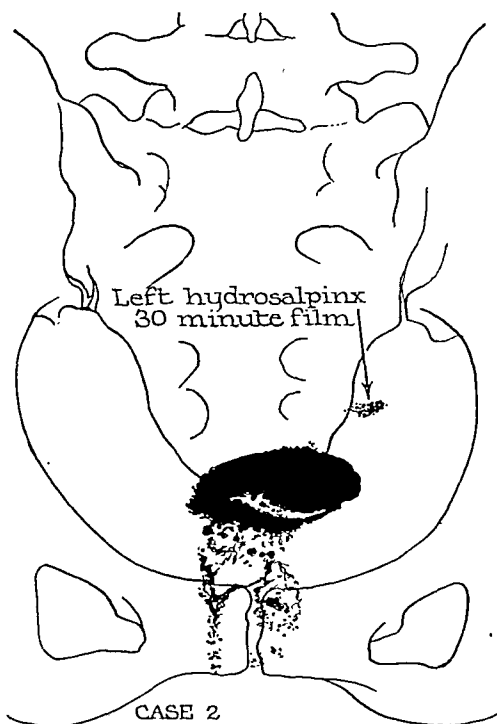


Fig. 4.—(Case 2.) Left hydrosalpinx thirty minutes after oil instillation. No evidence of "spill."

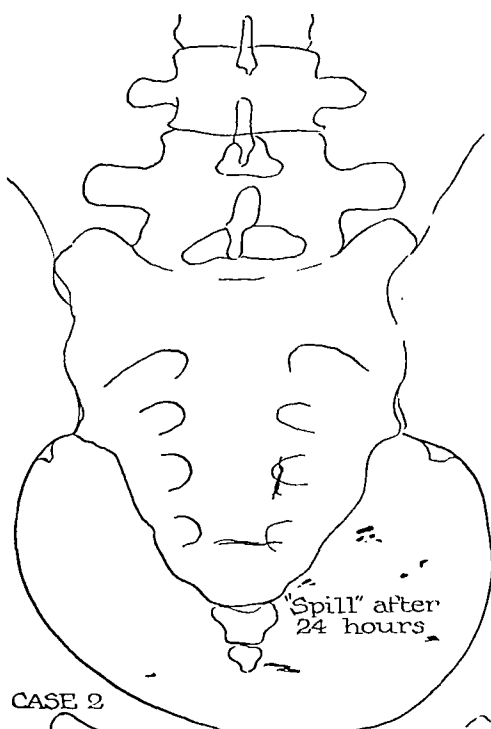


Fig. 5.—(Case 2.) Patency of left tube demonstrated by intraperitoneal "spill."

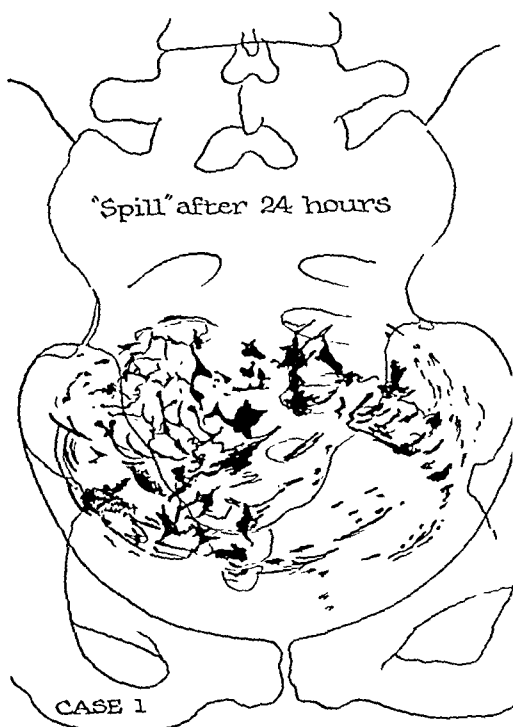


Fig. 2.—(Case 1.) Demonstrating final patency after twenty-four hours as shown by intraperitoneal "spill."

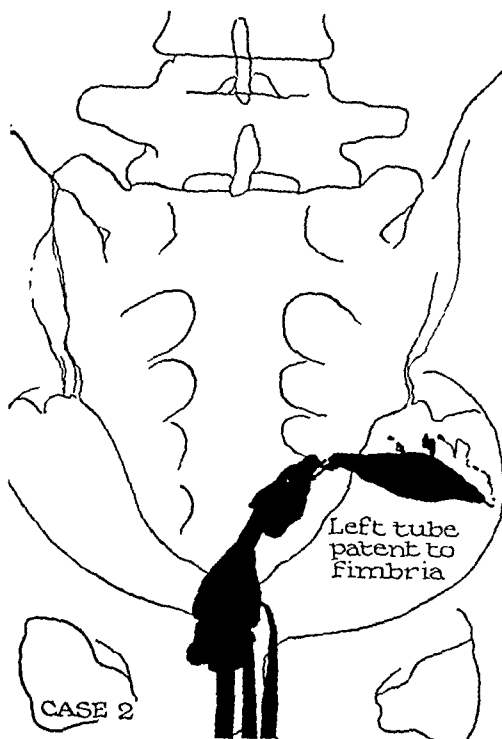


Fig. 3.—(Case 2.) Right cornual closure and left fimbrial closure to lipiodol. No patency demonstrated to gas. Acute suppurative appendicitis seven years previously.

of oil disclosed patency to the fimbriated ends, and twenty-four hours later "spill" was noted (Figs. 1 and 2). There were 13 such patients in whom pregnancy occurred within two months of the test.

Mrs. A. G., married two years and sterile one year, had an appendectomy for acute suppurative appendicitis seven years previously. On June 13, 1939, insufflation following coitus revealed no patency with three attempts to 200 mm. Hg pressure. On July 8 lipiodol instillation showed the right tube closed at the cornua and the left tube open to the fimbria (Fig. 3). A thirty-minute film showed a left hydrosalpinx (Fig. 4); a slight "spill" was demonstrated on the twenty-four-hour film (Fig. 5). The patient became pregnant two months later. The etiologic factor in tubal closure in this case was probably acute appendicitis.



CASE 3

Fig. 8.—(Case 3.) Illustrating the final passage of oil into the peritoneal cavity (thirty-hour film).

Mrs. M. P. was married one year and complained of sterility of six months' duration. Bimanual examination revealed a third-degree retroversion and adnexal tenderness. On Oct. 31, 1939, the tubes were negative to gas insufflation. On November 2 lipiodol instillation revealed a bilateral hydrosalpinx without evidence of "spill" (Figs. 6 and 7). A thirty-hour film showed marked bilateral "spill" (Fig. 8). Nine days after this procedure, the patient developed severe pain in the lower abdomen and a fever. Bimanual examination revealed a left adnexal mass, which was tender, fixed, and as large as the uterus. In spite of this, the patient conceived without an ensuing menstruation, and at eight weeks, the inflammatory mass had disappeared. At the examination six weeks after a normal confinement, the pelvic status was normal. This case illustrates the concomitant occurrence of pregnancy with the lighting up of an old pelvic inflammatory process, and demonstrates the value of oil in overcoming tubal obstruction.

DISCUSSION

The effect produced by insufflation which makes possible ensuing pregnancy may be explained almost entirely on a mechanical basis. The

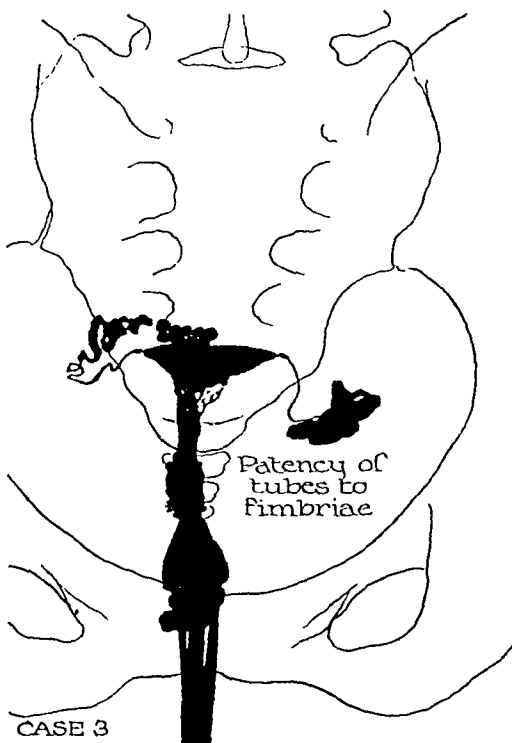


Fig. 6.—(Case 3.) Bilateral fimbrial closure with hydrosalpinx.



Fig. 7.—(Case 3.) Film taken thirty minutes after film shown in Fig. 6 and demonstrating a greater accumulation of oil in the dilated fimbriae. No true evidence of complete patency.

Rabbiner condemns the routine use of lipiodol and quotes several case reports by others showing the dangers encountered. On the other hand, many competent observers favor lipiodol over gas insufflation in determining tubal patency. Robins and Shapira studied the value of hysterosalpingography in 1,000 cases. They state that it gives much more information than insufflation and is attended with no harm in properly selected cases. They noted many instances where oil showed the tubes to be patent where gas could not pass through them. On repeating the insufflation subsequently they met with failure. They proved that oil has a therapeutic value in sterility by noting in autopsy specimens that under ordinary pressures, oil released adhesions and straightened out kinks of the tube. In 1,000 cases the only morbidity attributed to the instillation was the rupture of a large hydrosalpinx. The authors conclude that lipiodol does not harm the normal membrane of the uterus and tubes and does not set up peritoneal irritation. This view is shared by many others. White states that lipiodol seems to be of greater use than gas in the treatment of sterility, because the heavier oil exerts a more constant and prolonged hydrostatic pressure. Stein encountered no pelvic abscess nor any demonstrable morbidity in over 500 cases of lipiodol instillation. Reis and DeCosta did histologic studies on 30 Fallopian tubes removed at laparotomy which had been injected with lipiodol at varying periods before operation. In no instance could they demonstrate foreign body reaction.

In our series the value of lipiodol, after failure of insufflation to demonstrate patency, has been repeatedly shown. The successes have occurred under circumstances which point to the procedure as the therapeutic agent. We have used lipiodol in 85 cases of sterility and have noted the production of morbidity in only one patient, who developed an acute exacerbation of an old pelvic inflammatory process (Case 3). We believe that if contraindications are scrupulously observed, the use of lipiodol is attended by negligible morbidity. The discovery of a more readily absorbable radiopaque substance would undoubtedly diminish the ill effects described in many reports where lipiodol has remained in situ in enclosed cavities over prolonged periods.

SUMMARY AND CONCLUSIONS

1. Observations are recorded based on the investigation of the tubal patency test as a therapeutic measure in sterility.

2. In a series of 133 patients in whom the patency test could be evaluated, 54, or 40.6 per cent became gravid.

3. In 114, or 85.7 per cent, of the patients where patency in one or both tubes was demonstrated, 51, or 45 per cent, conceived. In 19, or 14.3 per cent, of the patients in whom no patency was demonstrated to gas or oil, 3, or 15.8 per cent, conceived.

4. Twenty-eight, or 21.5 per cent, patients became pregnant within two months of the test, the pregnancy being attributable directly to the procedure.

5. Coitus immediately preceding insufflation probably added to the high percentage of successes and was attended by no ill effects.

restoration of partial or complete patency in diseased tubes has been repeatedly demonstrated. It is not uncommon to encounter cases of tubal stenosis in which successive insufflations, either immediately or after an interval, show definite reduction in the pressure level at which patency becomes manifest. Obstructions such as inspissated mucus within the tubal lumen may be expelled, a tortuous tube may be straightened, and adhesions may be broken down. All these actions have been observed at laparotomy during which transuterine insufflation was performed. The peristaltic muscular action of the tube is stimulated by insufflation in a manner similar to the bowel stimulation brought about by intraluminal distention. This increased muscular activity enhances fertilization. Other factors which must be taken into consideration are the dislodgment of the cervical mucous plug by the cannula; ovulation induced by the mechanical stimulation of the cervix; and, if done, after coitus, the upward thrust of sperm into the uterine secretions toward the uterotubal ostia.

The value of perturbation in curing sterility is especially demonstrated in patients where some associated pathologic process causes interference with tubal function. In Rubin's series of cases (1932) partial obstruction or nonpatency was noted in 60 per cent of those who had had appendicitis, in 58 per cent of those with fibroids, in 82 per cent of those with a residual tube following ectopic pregnancy, and in 65 per cent of those with retroversion. As previously noted (Rubin), 21.6 per cent of a group of 570 patients with sterility who had some organic interference with tubal patency, became pregnant. Associated pathologic conditions which may have produced tubal obstruction in our series have been analyzed and presented in Table III. It is interesting to note that there were 2 patients in our series with third-degree retroversion in which no patency was demonstrated to gas or oil, but who nevertheless conceived, one without an ensuing menstruation and one within three months of the test. Two other successful patients with third-degree retroversion showed no patency to gas, and lipiodol "spill" was noted only after twenty-four hours. The value of oil in eventually overcoming tubal obstruction in these cases cannot be overlooked. Retroversion of the uterus is not uncommonly associated with sterility. Bonney has suggested that in some instances of retroversion, kinking of the tubes occurs, which may later become permanent due to organic shrinkage of the mesosalpinx. Examples of pregnancy following the patency test in patients with previous pelvic operations, previous appendicitis, and previous induced abortions were included in our series.

The relative value of gas insufflation and oil instillation has been the subject of much controversy. Rubin favors insufflation and uses lipiodol only occasionally. In 3,600 insufflations he found no serious complications, whereas in 132 cases with lipiodol instillation he noted 6 patients with mild peritoneal reaction and 3 who developed pelvic abscesses requiring operative intervention. King favors gas insufflation which he used in 300 reported cases without mishap and reserves the use of lipiodol for cases where extra information is needed in closed tubes.

pregnancies resulted with two repeat pregnancies following subsequent lipiodol injections. Where tubes were normal but uteri were abnormal (9 patients: didelphic uterus 3, postoperative inversion 1, and submucous fibroma 5), 3 pregnancies resulted.

The age of 5 patients was beyond 40 years, and not any of these became pregnant. Two husbands were sterile. Ten patients had closed tubes. After considering all patients in whom pregnancy might occur, we find in this last group that 48, or more than 50 per cent, became pregnant following lipiodol injections. From the time of the lipiodol injection to the last menstrual period in 35, or 70 per cent, of the pregnant patients, less than one month up to four months intervened. To me this is the best proof of the efficacy of the procedure.

DR. J. MILTON SINGLETON, KANSAS CITY, MO.—I wonder whether the writers do not feel that the time of insufflation, immediately or shortly after coitus, might not lead to increased incidence of ectopic and ovarian pregnancy. I have selected for my insufflations the fourth or fifth day after menstruation, when there is no danger of blowing the sperm up into the tube and consequent danger of producing an ectopic pregnancy.

I believe with the widely increasing use of vaginal plugs at menstruation that we are going to see a marked increase in the incidence of retrograde menstruation, chemical salpingitis, and hence in the incidence of sterility.

DR. SOLOMON (closing).—We do not believe that there is a higher incidence of ectopic pregnancy following the therapeutic use of gas or oil. In our series there were two instances of tubal pregnancy following perturbation.

We do not believe that lipiodol is irritating to the peritoneum if proper contraindications to the test are observed. Forsdike of London reports many laparotomies performed from a few days to a few years after the use of lipiodol, and in none did he observe any evidence of peritoneal irritation. Most of the oil is absorbed in a week or ten days, and a flare-up may occur only when there is obscure acute or subacute inflammatory disease present.

We can account for no instance of infection attributable to the preliminary coitus in our series, and feel that it is important therapeutically.

6. An analysis of the pathologic conditions which contribute to tubal obstruction is presented.

7. The cure of sterility in tubal obstruction is accomplished by a re-establishment of tubal function and patency due to the mechanical effects of perturbation.

8. The relative merits of insufflation and lipiodol instillation as therapeutic agents are considered. We believe that lipiodol instillation is superior to gas insufflation both from a diagnostic and therapeutic standpoint.

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DISCUSSION

DR. ROLAND S. CRON, MILWAUKEE, WIS.—In principle and practice I agree with the writers in all respects except that we do not routinely arrange that the patency test be preceded by coitus. This does not seem to have influenced the incidence of conception for as you will observe about 50 per cent of our sterile women became pregnant.

Dr. Reuben Peterson and his associates first reported the therapeutic value of this test in 1922 at the St. Louis meeting of the A. M. A. In that report I recorded the first pregnancy that had occurred immediately following a gas insufflation. The following year, 1923, at the San Francisco meeting we presented the results obtained in the study of 36 sterile women. Pregnancy occurred in 13, or 36 per cent, of the women who had been insufflated.

Since 1935 gas insufflation has been used on not more than one out of every five patients. My conversion to lipiodol was due to the fact that tubes found to be impervious to carbon dioxide repeatedly became patent to an oily substance at pressures below that used for gas insufflations. Second, more patients, and many of those previously insufflated, become pregnant. Third, peritoneal reactions to lipiodol when minimum quantities, 5 to 7.5 c.c., were introduced, were no more common than after gas. Fourth, one can learn more about the condition of the uterus, tubes, and ovaries than is the case with gas insufflations.

In 1929 a study of sterility patients who were treated with carbon dioxide insufflations showed an incidence of 25 per cent successful pregnancies. In 1938 a review of 100 patients in whom pregnancy might occur because of tubes proved patent by use of lipiodol, showed that 39 per cent conceived.

The present review which covers a period from 1936 to 1940 is based on the study of 123 sterile couples. Where tubes were normal and open in 55 patients, 33 pregnancies resulted. Where tubes were abnormal and open in 33 patients, 12

stimulated. There is also the question as to whether active immunization of the pregnant mother will result in active immunization of the fetus in utero and, if so, how long will such immunity persist after birth. Since there is a general increased activity of the bodily functions during pregnancy, the possibility exists that antibody formation might also be stimulated.

In order to obtain an answer to some of the foregoing questions, and because the diphtheria antitoxin level in the human pregnant mother has been followed through pregnancy only in isolated instances, and as far as is known, active immunization of the human pregnant mother has not been attempted in order to determine the effect on the mother, newborn infant, and the placenta, the following experiments were carried out.

METHODS

The subjects chosen for this problem were in the latter part of the second trimester of their pregnancy. All mothers were Schick tested on admission, 0.1 c.c. of the standard Schick test toxin being used. All Schick tests were controlled with heated toxin. At the same time that the patient received the Schick test, blood was obtained from the cubital vein for the determination of the diphtheria antitoxin titer. The Schick tests were read at the end of seventy-two hours and again at the end of a week. Schick positive and Schick negative mothers were actively immunized with diphtheria toxoid and an equal number were used as a control. The mothers immunized received five subcutaneous injections at weekly intervals, beginning with 0.1 c.c., then 0.25, 0.5, 1.0, and 2.0 c.c., respectively, of the diphtheria toxoid. Blood determinations for diphtheria antitoxin were made at monthly intervals so that each patient had three or four determinations by the time of delivery of the newborn infant. Upon delivery, fetal blood was obtained from the umbilical cord for diphtheria antitoxin determinations.

Diphtheria antitoxin determinations were also made on a group of non-Schick tested, nonimmunized mothers followed through their course of pregnancy as a control on the stimulating effect of the Schick test material.

The infants were Schick tested some time during the first week of life, usually on the sixth day.

The tests for diphtheria antitoxin were made by the intracutaneous test in rabbits, using the Moss-Jones modification of the test reported by Fraser.^{11*}

Immediately following delivery of the newborn infant, the placenta was emptied of its residual blood as completely as possible. This was carried out by frequently stripping the placental cord, 50 to 125 c.c. of blood usually being obtained.

Each placenta was weighed and then extracted according to the method of McKhann.¹² Briefly the method is as follows:

The placenta is ground in a meat grinder and extracted with a 4 per cent salt solution. The mixture of placental tissue in salt solution is passed through cheesecloth and the filtrate centrifuged. After centrifugation, ammonium sulfate is added to make a 50 per cent saturation. This results in the precipitation of the globulins. The precipitate is dialyzed, filtered, and passed through a Berkefeld filter. Diphtheria antitoxin determinations were made on the final filtrate.

RESULTS

Schick Tests.—Fifty-two and eight-tenths per cent of the mothers gave a positive Schick test. A small number gave a pseudoreaction. In a few of the patients, there was a combined Schick reaction. Only a small number of those Schick tested reacted rather severely to the test. They complained of an intense itching and de-

*These tests were carried out by Eli Lilly & Company Research Laboratories.

THE OCCURRENCE OF DIPHTHERIA ANTITOXIN IN THE HUMAN PREGNANT MOTHER, NEWBORN INFANT, AND THE PLACENTA*

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INTRODUCTION

MUCH has been written on the placental transfer of antibodies. As early as 1879 Burekhardt¹ attempted to protect the fetus against variola by vaccination of the pregnant mother. He felt that intra-uterine vaccination would protect the infant against smallpox.

Fischl and Wundschheim² on examining cord blood found diphtheria antitoxin present in a good proportion of specimens. In 1904 Polano³ reported on a study of the passive transfer of diphtheria antitoxin from mother to child. He found that, by giving the pregnant mother antitoxin some days previous to delivery, he was able to demonstrate the presence of the antitoxin in the cord blood. Staubli,⁴ von Groer and Kassowitz⁵ and numerous other investigators have demonstrated that antibodies are transferred to the fetus whether the mother is actively or passively immunized. In spite of the abundance of evidence of the placental transfer of antibodies, some of the earlier investigators were of the opinion that such transfer did not occur through a normal placenta and that the antibodies found in fetal blood were produced by fetal tissues. Bourquin's⁶ work on the permeability of the placenta to agglutinins, hemolysins, diphtheria antitoxin and diastase has done much to disprove this concept of the earlier investigators. Kuttner and Ratner⁷ in addition to confirming the permeability of the human placenta to antibodies, showed that the ingestion of colostrum did not increase the antibody content in the blood stream of the infant. More recent contributions to this line of investigation have been made by Ogawa,⁸ who found that the amount of antitoxin in the sera of the offspring of actively immunized rabbits was proportional to that in the mother; by Richardson,⁹ who demonstrated the presence of diphtheria antibacterial antibodies as well as antitoxin in mothers and offspring of guinea pigs actively immunized against diphtheria and by Neill, Gaspari, Richardson and Sugg¹⁰ who studied the diphtheria antibacterial antibodies and antitoxin in a mother with an unusually high degree of immunity and found that the diphtheria-antibacterial antibodies, as well as the antitoxin, were transmitted to the infant if present in the mother.

The fact that the placenta acts as a "go between" for the transmission of antibodies from the maternal to the fetal side raises many questions. It is of interest to determine to what extent the placenta is permeable to antibodies circulating in the maternal blood stream; whether such antibodies are transferred to the fetus in equal strength or are filtered out in passing through the placenta; to what extent, if at all, the placenta retains such antibodies and whether it is possible that placental tissue may have the property of antibody formation when properly

*Read at the Chicago Gynecological Society, November 15, 1940.

TABLE II. DIPHTHERIA ANTITOXIN LEVELS IN NONIMMUNIZED MOTHERS AND NEWBORN INFANTS

Original Antitoxin Titer Level > 0.002 u/c.c.* Serum

CASE	HISTORY OF DIPHTHERIA	SCHICK TEST	ORIGINAL TITER	8 MO.	9 MO.	TERM	WEEKS AFTER DETERMINATION	FETAL BLOOD	SCHICK TEST ON INFANT
2	+	-	0.1	0.1	0.5	0.2	11	1.0	-
4	Exposure	±	0.01	1.0	1.0	1.0	14	1.0	-
7	-	-	0.01	1.0	0.5	0.002	14	1.0	-
8	-	-	0.2	1.0	0.5	1.0	13	0.5	-
10	-	+	0.01	2.0		1.0	9	Stillbirth	
11	-	-	0.01	2.0		2.0	10	2.0	-
13	-	±	0.01	2.0	2.0	2.0	15	5.0	-
14	-	-	0.1	0.2		0.2	10	0.2	-
18	-	-	0.01	2.0		2.0	20	Stillbirth	
19	-	±	0.1	1.0		1.0	22	0.5	-
20	-	±	0.2	10.0	10.0	0.1	11	10.0	-
21	-	±	0.01	1.0	1.0	1.0	20	2.0	-
22	-	±	0.1	2.0		2.0	19	2.0	-
23	-	-	0.05	2.0	1.0	1.0	13	2.0	-
25	-	-	0.005	1.0		1.0	8	1.0	-
26	+	-	0.1	5.0		1.0	26	2.0	-
27	-	-	0.05	0.05	0.05	0.1	21	0.1	-

*“u” equals units of antitoxin.

TABLE III. DIPHTHERIA ANTITOXIN LEVELS IN NON-SCHICK TESTED NONIMMUNIZED MOTHERS

Units per c.c. Serum			
Diphtheria Antitoxin Titer Level			
CASE	7 MO.	8 MO.	9 MO.
1	0.2	0.2	0.2
3	0.2	0.2	0.2
4	0.5	0.5	0.5
5	0.02	0.02	0.02
9	0.2	0.2	0.2
10	0.2	0.2	0.2
13	0.1	0.1	0.1
2	0.002	0.002	0.002
6	0.002	0.002	0.002
7	0.002	0.002	0.002
8	0.002	0.002	0.002
11	0.002	0.002	0.002
12	0.002	0.002	0.002

Schick test material. This was borne out by the results obtained on a small group of non-Schick tested, nonimmunized mothers followed during their course of pregnancy. In this group, as illustrated by Table III, there were no changes in the antitoxin level. This is in accord with the investigations of Fraser and Halpern¹⁴ who found that Schick material stimulates antitoxin production in individuals with an antitoxin level greater than 0.002 of a unit per cubic centimeter of serum and that the response, when it occurs, is rapid. This fact is well illustrated by the findings shown in Table I. These investigators also found that non-Schick tested, nonimmunized individuals, possessing natural antitoxin, gave no change in the titer level over a period of years.

From the above, it can be stated that the transfer through the placenta of natural diphtheria antitoxin, when possessed by the mother, will provide the newborn infant

veloped a rather marked erythema, followed by vesiculation, desquamation, and pigmentation. The blood serum diphtheria antitoxin determinations were found to be in accord with the Schick test results. Schick positive individuals contained 0.002 of a unit or less of diphtheria antitoxin per cubic centimeter of blood serum. This confirms the work of Brandon and Fraser¹³ who have shown that the antitoxin blood level for Schick-immunity lies between 0.002 and 0.004 of a unit of antitoxin per cubic centimeter of serum.

Nonimmunized Mothers and Infants.—The results of the control group of non-immunized mothers with positive Schick tests showed a low antitoxin content in the blood. The titer remained at the same level throughout the pregnancy in all but one patient (Table I). In Case 9, there was some rise in the antitoxin level as pregnancy neared term.

Fraser and Halpern,¹⁴ reporting on a group of Schick positive nonimmunized adults, found that there was no rise in the antitoxin-level when it was 0.002 of a unit or less per cubic centimeter of serum. They feel that Schick positive and non-immunized individuals developing a rise in the titer level are exceptions and that these persons have amounts of antitoxin which are not detected at the 0.002th level of titration. Case 9 would have to be classed as such an exception, as this patient had a positive Schick, 0.002 of a unit of diphtheria antitoxin per cubic centimeter of serum at seven months, 2.0 units at eight months, 2.0 units at nine months, and 2.0 units at term.

Schick positive mothers, showing no change in the antitoxin titer during the course of their pregnancy, gave birth to infants that were Schick positive and whose antitoxin level was the same as that of the mother (Table I).

TABLE I. DIPHTHERIA ANTITOXIN LEVELS IN NONIMMUNIZED MOTHERS AND NEWBORN INFANTS

Original Antitoxin Titer Level 0.002 u/c.c.* Serum or Less

CASE	HISTORY OF DIPHTHERIA	SCHICK TEST	ORIGINAL TITER	8 MO.	9 MO.	TERM	WEEKS AFTER DETERMINATION	FETAL BLOOD	SCHICK TEST ON INFANT
1	-	+	0.002	0.002	0.002	0.002	13	0.002	+
3	-	+	0.002	0.002	0.002	0.002	11	0.002	+
5	-	+	0.002	0.002	0.002	0.002	11	0.002	+
6	-	+	0.002	0.002	0.002	0.002	13	0.002	+
9	-	+	0.002	2.0	2.0	2.0	10	1.0	±
12	-	+	0.002	0.002	0.002	0.002	14	0.002	+
15	-	+	0.002	0.002	0.002	0.002	16	0.002	+
16	-	+	0.002	0.002	0.002	0.002	18	0.002	+
17	-	+	0.002	0.002	0.002	0.002	23	0.002	+
28	-	+	0.002	0.002	0.002	0.002	11	0.002	+
31	-	+	0.002	0.002		0.002	12	0.002	+

*"u" equals units of antitoxin.

The antitoxin titer of the controls with negative Schick tests showed a gradual increase in the antitoxin level as pregnancy neared term (Cases 4, 8, 11, 13, etc., Table II). Some of the patients showed a decrease in the antitoxin level before term (Cases 2, 10, 23, and 26, Table II) and in only two instances (Cases 7 and 20) did that decrease fall below the level of the first determination.

Control mothers with negative Schick tests gave birth to infants with negative Schick tests and an antitoxin level equal to (Cases 4, 11, 14, etc.), higher (Cases 2, 7, 13, 20, etc.), and, in two patients (Cases 8 and 19), lower than that of the mothers' blood at term. The antitoxin level of the infants in these cases was always higher than the preliminary antitoxin level of the mother.

The rise in the antitoxin titer level during the course of pregnancy in the control group of mothers may be attributed to the accelerating effect of the toxin in the

there was a rise in the antitoxin titer at term, this being 5 to 2,500 times that of the original titer. In only two patients (Cases 13 and 29) was there no rise in the antitoxin concentration in the blood serum of the mothers followed during their course of pregnancy.

The Schick negative mothers showed a hyperactive response to antibody formation. All mothers (Table V) had a high antitoxin titer at term. This increase varied from 50 to 5,000 times the original titer value. In some cases, this increase remained throughout pregnancy (Cases 4, 9, 14, 20, Table V) and in others, it was depleted at term but was never back to the pre-immunization value (Cases 5, 10, 17, Table V).

The length of time elapsing between the first immunizing dose of toxoid and the last diphtheria antitoxin titer determination in the Schick positive and Schick negative group of mothers, apparently, played no part in the quantity of antitoxin formed, as the maximum concentration in both was reached in four to eight weeks after immunization was begun (Cases 6 and 31, Table IV, and Cases 4 and 27, Table V). This is not in accordance with the general opinion that the peak of immunity is attained in three to six months.

The infants born to the actively immunized Schick positive and negative mothers gave negative Schick tests and in most instances had an antitoxin titer level equal to that of the mothers at term (Tables IV and V).

Placental Extracts.—Antitoxin determinations were made upon placental extracts of both immunized and nonimmunized mothers to determine, if possible, whether the placenta acted merely to transfer substances to the fetus, whether antibodies are stored in its tissue, or whether the tissue itself is capable of antibody formation when properly stimulated.

TABLE VI. A COMPARISON OF THE MATERNAL, FETAL AND PLACENTAL ANTITOXIC VALUES IN THE NONIMMUNIZED GROUP OF PREGNANT MOTHERS

Original Antitoxin Titer Level 0.002 u/c.c.* Serum or Less

CASE	MATERNAL DIPH- THERIA ANTITOXIN TITER U/C.C. SERUM AT TERM	FETAL DIPH. ANTITOXIN TITER U/C.C. SERUM AT BIRTH	DIPH. ANTITOXIN TITER U/C.C. OF PLACENTAL EXTR.	GRAM WT. OF PLA- CENTA	DIPH. ANTITOXIN TITER U/GM. PLACENTAL TISSUE	TOTAL UNITS OF DIPH. ANTITOXIN IN THE PLACENTA	C.C. OF FETAL BLOOD \approx TO TOTAL PLACENTAL UNITS
1	<0.002	<0.002	<0.002	450.4	0.0000	0.000	0.0
3	0.002	0.002	0.002	630.0	0.0005	0.315	157.5
5	0.002	0.002	0.002	463.0	0.0008	0.370	185.2
6	<0.002	<0.002	0.002	462.0	0.0017	0.785	392.7
9	2.0	1.0	0.2	466.3	0.0514	23.96	23.96
12	<0.002	0.002	<0.002	770.0	0.0000	0.000	0.00
17	<0.002	<0.002	0.002	638.8	0.0014	0.910	455.0
28	<0.002	<0.002	0.002	527.8	0.0014	0.76	380.00

*"u" equals units of antitoxin.

In the Schick positive nonimmunized group of mothers that had 0.002 units or less of antitoxin per cubic centimeter of blood (Table VI), the amount of antitoxin per gram of placenta corresponded, in most cases, very closely to the amount present in the maternal and fetal blood. In only 3 cases (6, 17 and 28) was a small amount of antitoxin found in the placenta when none was detectable in the maternal or fetal blood. This could probably be explained by the fact that the antitoxin in the placental extract is increased in concentration as a result of the method of extraction.

TABLE IV. DIPHTHERIA ANTITOXIN LEVELS IN ACTIVELY IMMUNIZED MOTHERS AND NEWBORN INFANTS

Original Antitoxin Titer Level 0.002 u/c.c.* Serum or Less

CASE	HISTORY OF DIPHTHERIA	SCHICK TEST	ORIGINAL TITER	8 MO.	9 MO.	TERM	WEEKS AFTER DETERMINATION	FETAL BLOOD	SCHICK TEST ON INFANT
1	-	+	0.002	0.002	0.01	0.002	10	0.02	-
2	-	+	0.002	1.0	1.0	0.5	16	0.002	-
6	-	±	0.002	5.0	0.1	5.0	12	5.0	-
7	-	+	0.002	0.1	0.2	0.2	17	0.2	-
12	-	+	0.002	10.0	5.0	1.0	17	5.0	-
13	-	+	0.002	0.002	0.02	0.002	12	0.002	-
15	-	-	0.002	0.1	0.2	0.2	11	0.2	-
16	-	+	0.002	10.0	5.0	5.0	15	10.0	-
18	-	+	0.002	0.002	0.002	0.01	14	0.01	-
21	-	+	0.002	0.1	0.2	0.2	18	0.5	-
24	-	+	0.002	0.05	0.1	0.1	15	0.2	-
25	-	+	0.002	0.002	0.01	0.01	18	0.002	-
29	-	+	0.002	0.002		0.002	10	0.002	-
31	-	+	0.002	0.002	0.005	0.02	20	0.02	-

*“u” equals units of antitoxin.

with a passive immunity. It is also apparent that the mere Schick testing of the pregnant mother possessing natural antitoxin will act in most cases as a stimulus to increase antitoxin production and provide possibly a greater and more prolonged protection to the infant after birth.

Immunized Mothers and Infants.—In the actively immunized group of mothers with positive Schick tests, the antitoxin response varied with each individual as regards the rapidity and quantity of the increase. In most instances (Table IV),

TABLE V. DIPHTHERIA ANTITOXIN LEVELS IN ACTIVELY IMMUNIZED MOTHERS AND NEWBORN INFANTS

Original Antitoxin Titer Level > 0.002 u/c.c.* Serum

CASE	HISTORY OF DIPHTHERIA	SCHICK TEST	ORIGINAL TITER	8 MO.	9 MO.	TERM	WEEKS AFTER DETERMINATION	FETAL BLOOD	SCHICK TEST ON INFANT
3	-	±	0.2	50.0	50.0	20.0	15	50.0	-
4	-	-	0.01	50.0		50.0	8	20.0	-
5	-	-	0.01	50.0		10.0	8	20.0	-
8	carrier	-	0.1	10.0		5.0	21	5.0	-
9	-	-	0.1	20.0	20.0	20.0	20	20.0	-
10	-	-	0.01	10.0		5.0	10	10.0	-
11	-	±	0.1	50.0	10.0	10.0	13	20.0	-
14	-	-	0.0	20.0	20.0	20.0	11	20.0	-
17	-	±	0.1	50.0		20.0	10	20.0	-
19	-	-	0.2	100.0		50.0	22	100.0	-
20	-	-	0.5	20.0	20.0	20.0	19	50.0	-
22	-	-	0.2	10.0	5.0	5.0	16	10.0	-
23	-	-	0.2	5.0		5.0	13	5.0	-
26	-	-	0.05	10.0		10.0	27	10.0	-
27	-	-	0.2	10.0		10.0	25	10.0	-
28	-	+	0.2		10.0	10.0	22	10.0	-
30	-	-	0.2	20.0		20.0	16	20.0	-
32	-	±	0.2			50.0	8	50.0	-
33	-	-	0.1	5.0		10.0	12	20.0	-
34	-	±	1.0		20.0	10.0	12	20.0	-

*“u” equals units of antitoxin.

29 (Table VIII) are the only ones in which the placenta contained more antitoxin per gram than did the fetal or maternal blood. These results suggest that occasionally a placenta may store (or form) a small amount of antitoxin. Furthermore, a slight amount of storage could easily be obscured by the enormous increase that occurs in the blood of some of the actively immunized mothers.

TABLE VIII. A COMPARISON OF THE MATERNAL, FETAL AND PLACENTAL ANTITOXIC VALUES IN THE ACTIVELY IMMUNIZED GROUP OF PREGNANT MOTHERS

Original Antitoxin Titer Level 0.002 u/c.c.* Serum or Less

CASE	MATERNAL DIPH- THERIA ANTITOXIN TITER U/C.C. SERUM AT TERM	FETAL DIPH. ANTITOXIN TITER U/C.C. SERUM AT BIRTH	DIPH. ANTITOXIN TITER U/C.C. OF PLACENTAL EXTR.	GRAM WT. OF PLA- CENTA	DIPH. ANTITOXIN TITER U/GM. PLACENTAL TISSUE	TOTAL UNITS OF DIPH. ANTITOXIN IN THE PLACENTA	C.C. OF FETAL BLOOD \approx TO TOTAL PLACENTAL UNITS
1	0.02	0.02	0.01	433.0	0.008	3.4	170.0
2	0.5	<0.002	0.2	397.2	0.055	22.0	11000.0
6	5.0	5.0	1.0	448.6	0.490	220.0	44.0
7	0.2	0.2	0.1	572.4	0.008	4.98	24.9
12	1.0	5.0	0.2	492.4	0.136	67.1	13.42
13	0.002	<0.002	0.01	681.2	0.002	2.0	1000.0
15	0.2	0.2	0.2	593.6	0.086	51.0	255.0
16	5.0	10.0	0.5	542.2	0.533	300.0	30.0
18	0.01	0.01	0.1	598.4	0.095	55.5	5550.0
21	0.2	0.5	0.5	619.6	0.34	211.5	423.0
24	0.1	0.2	0.01	496.7	0.008	4.29	21.45
29	<0.002	<0.002	0.002	568.2	0.001	0.99	496.0
31	0.02	0.02	0.002	519.1	0.001	0.93	46.7

*"u" equals units of antitoxin.

TABLE IX. A COMPARISON OF THE MATERNAL, FETAL AND PLACENTAL ANTITOXIC VALUES IN THE ACTIVELY IMMUNIZED GROUP OF PREGNANT MOTHERS

Original Antitoxin Titer Level > 0.002 u/c.c.* Serum

CASE	MATERNAL DIPH- THERIA ANTITOXIN TITER U/C.C. SERUM AT TERM	FETAL DIPH. ANTITOXIN TITER U/C.C. SERUM AT BIRTH	DIPH. ANTITOXIN TITER U/C.C. OF PLACENTAL EXTR.	GRAM WT. OF PLA- CENTA	DIPH. ANTITOXIN TITER U/GM. PLACENTAL TISSUE	TOXIN IN THE PLACENTA	C.C. OF FETAL BLOOD \approx TO TOTAL PLACENTAL UNITS
3	20.0	50.0	5.0	485.4	2.15	1045.0	20.9
4	50.0	20.0	2.0	525.0	1.35	710.0	35.5
5	10.0	20.0	1.0	556.5	0.287	160.0	8.0
8	5.0	5.0	1.0	489.4	0.868	425.0	85.0
9	20.0	20.0	1.0	442.4	0.96	425.3	21.2
10	5.0	10.0	0.5	349.4	0.49	170.8	17.08
11	10.0	20.0	0.002	600.4	0.0015	0.929	0.046
14	20.0	20.0	5.0	448.4	1.78	800.0	40.0
17	20.0	20.0	5.0	581.0	1.24	724.0	36.25
19	50.0	100.0	10.0	490.4	9.31	4566.6	45.66
20	20.0	50.0	2.0	688.9	1.48	1020.0	20.4
22	5.0	10.0	1.0	609.1	0.87	532.6	53.26
23	5.0	5.0	1.0	550.8	0.76	420.0	84.0
32	50.0	50.0	5.0	547.0	3.2	1755.0	35.1
33	10.0	20.0	1.0	529.0	0.72	381.3	19.06
35	10.0	20.0	1.0	450.9	0.86	390.0	19.5

*"u" equals units of antitoxin.

TABLE VII. A COMPARISON OF THE MATERNAL, FETAL AND PLACENTAL ANTITOXIC VALUES IN THE NONIMMUNIZED GROUP OF PREGNANT MOTHERS

Original Antitoxin Titer Level > 0.002 u/c.c.* Serum

CASE	MATERNAL DIPH- THERIA ANTITOXIN TITER U/C.C. SERUM AT TERM	FETAL DIPH. ANTITOXIN TITER U/C.C. SERUM AT BIRTH	DIPH. ANTITOXIN TITER U/C.C. OF PLACENTAL EXTR.	GRAM WT. OF PLA- CENTA	DIPH. ANTITOXIN TITER U/GM. PLACENTAL TISSUE	TOTAL UNITS OF DIPH. ANTITOXIN IN THE PLACENTA	C.C. OF FETAL BLOOD \approx TO TOTAL PLACENTAL UNITS
2	0.2	1.0	0.02	717.5	0.009	6.6	6.6
4	1.0	1.0	0.1	516.4	0.061	31.75	31.75
8	1.0	0.5	0.5	446.0	0.357	159.22	318.44
11	2.0	2.0	0.2	513.8	0.144	74.14	37.07
13	2.0	5.0	0.5	660.0	0.355	221.6	44.32
14	0.2	0.2	0.05	562.1	0.039	22.24	111.2
19	1.0	0.5	0.2	464.4	0.157	73.3	146.6
20	0.1	10.0	1.0	707.8	0.492	348.23	34.82
21	1.0	2.0	0.1	528.2	0.096	40.97	20.48
22	2.0	2.0	0.02	432.0	0.019	8.47	4.23
23	1.0	2.0	0.2	684.9	0.111	76.64	38.32
25	1.0	1.0	0.2	521.7	0.207	108.5	108.5
26	1.0	2.0	0.1	474.7	0.096	45.8	22.9

*"u" equals units of antitoxin.

In the nonimmunized Schick negative group that contained 0.002 units of antitoxin or more per cubic centimeter of blood serum, the amount of antitoxin per gram of placenta was very small in all cases (Table VII), except one, as compared with the number of units per cubic centimeter in the maternal and fetal blood. Case 20 had about five times more antitoxin per gram of placenta than the maternal blood, but had one-twentieth that of the fetal blood. This is the only case also in which there was an excessively greater amount of antitoxin in the fetal blood than in the maternal blood. When the average amount of diphtheria antitoxin in the blood serum of all the mothers is compared with the average amount of antitoxin in all of the placenta, the blood serum possesses about sixteen times as much antitoxin per cubic centimeter of blood serum as the placenta does per gram of tissue.

These results indicate that the placenta normally contains only small amounts of diphtheria antitoxin and that in those mothers in whom there was no increase in the blood antitoxin during pregnancy, the amount per gram of placenta more closely approximates the amount per cubic centimeter of blood serum than in those in which there was a slight rise.

The results on the actively immunized mothers present much the same picture (Tables VIII and IX). In the Schick positive group, which had original titers of 0.002 units or less, there was an average of about 7.8 times as much antitoxin per cubic centimeter of blood serum as in 1 Gm. of placental tissue. In the actively immunized group of Schick negative mothers having original titers of 0.002 units or more, the serum contained an average of fourteen times as much antitoxin per cubic centimeter as did 1 Gm. of placenta.

There is very little evidence in these results to indicate that the placenta either stores or forms appreciable amounts of diphtheria antitoxin following active immunization. The amount of antitoxin in the placenta rises following immunization but not in proportion to the rise in the antitoxin level of the blood. In fact, in many cases, the total amount of antitoxin in the placenta can be accounted for on the basis of the retention of a small amount of fetal and maternal blood, since it was impossible to remove the blood completely from the placenta. With increase in the blood serum level, this factor becomes more appreciable. Cases 2, 13, 18, 21, and

4. Schick positive and negative mothers, actively immunized, showed a marked response in the formation of antitoxin, in some cases as much as 5000 times the pre-immunization level being reached.

5. Infants born to the actively immunized mothers gave negative Schick tests and had antitoxin level, in most cases, equal to that of the mothers at term.

6. The maximum antitoxin level in the mothers' blood was reached in a period of four to eight weeks.

7. Relative "blood free" placentas of immunized and nonimmunized mothers, when extracted for diphtheria antitoxin, yielded, in most cases, insignificant amounts.

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DISCUSSION

DR. ROBERT A. BLACK.—The diphtheria question is by no means settled. Bieber immunized 1,097 children out of a group of 3,000 and found four who contracted the disease. Greengard in his studies felt that the giving of toxoid before three months of age did very little good. Eighty-four per cent of fetuses at birth have been found to have antitoxin in the blood, a figure that falls off gradually until at eighteen months it was 32 per cent, and at two and one-half years it was 28 per cent. With these figures in mind you wonder whether trying to immunize through the mother would be really worth while.

In order to find out whether Dr. Schmitz was doing something that was rather useless, I looked up some death rates. There are 49,000 to 50,000 infants born in Chicago each year. During the past ten years we had 2 deaths in Chicago from diphtheria in infants under six months. Incidentally there have been no deaths from diphtheria in the six-month-old infants in four years. In looking up the incidence of diphtheria in the yearling, we found that there were 251 cases of diphtheria with 36 deaths. If Dr. Schmitz can immunize these babies he has made a great step forward.

If Dr. Schmitz could get whooping cough antibodies to be effective through the placenta he will have made another contribution to pediatrics.

One thing occurred to me that might explain some of the discrepancies in the report. Dr. Schmitz noted, for example, in No. 9, from $\frac{1}{200}$ to $\frac{1}{25}$ unit of toxin in the blood. I wonder if he took a culture on the mother's throat, for the mother might have acquired diphtheria.

There is a great deal of talk of colostrum being one of the fluids that carries immunizing bodies or antibodies into the infant. It would be interesting to check this point.

DR. JAMES CONNER.—It is a bit out of the ordinary to find 52 per cent of positive Schick tests in adults. The majority of workers insist that at least 90 per

DISCUSSION

It was the intention of this investigation to determine the part played by the placenta in the transfer of diphtheria antitoxin from the non-immunized and actively immunized human pregnant mother to her offspring and also to evaluate placental extracts as a source of antibody.

It was found that the placentas of the nonimmunized and immunized group of mothers were permeable to the circulating antitoxin of the mother and it was passed on to the fetus, in nearly all cases, in equal strength. As the literature reveals, this fact has been observed and pointed out for a number of years.

Although many mothers possess natural antitoxin, it is of a low value. If the duration of prophylaxis is dependent upon the amount of circulating antibodies, the mere Schick testing of the mothers possessing a Schick-immunity level, will result in a rise in the antitoxin concentration. This in turn will be transferred to the newborn and will probably provide a more lasting passive immunity.

The marked increase in the antitoxin concentration of the blood serum of the actively immunized mothers and its transfer to the infant will certainly provide a more lasting immunity to the newborn. Whether we have succeeded in the active immunization of the fetus in utero by actively immunizing the pregnant mother is impossible to determine at the present time. More information on this question will become available, it is hoped, after the newborn infants have been followed over a period of one to two years.

The results on the placental extracts were exceedingly interesting, inasmuch as placental extracts have been extensively used as a prophylactic against measles.

It was found that the placenta of nonimmunized and actively immunized mothers contained very little diphtheria antitoxin when compared to the amount present in the blood serum of the mother and that this amount, in most cases, could easily be accounted for by residual maternal-fetal blood in the placenta. This fact may well account for the value attached to the placental extracts for measles immune globulin as in this extract, as described by McKhann,¹² the placenta is not emptied of its retained blood but it is included in the extract. Possibly the protective value that might be derived from such an extract could be obtained by merely using convalescent serum or pooled adult whole blood, as Grod¹⁵ found that retroplacental blood exercised the same influence on the course of measles as did serum from adults or placental extract.

CONCLUSIONS

1. Nonimmunized, Schick positive mothers showed no rise in the antitoxin level during their course of pregnancy.
2. Nonimmunized, Schick negative mothers all showed a rise in the antitoxin content during their course of pregnancy.
3. Infants born to Schick positive mothers were usually Schick positive and had an antitoxin content, in most instances, equal to that of the mothers at term.

The transfer of antitoxin by way of the colostrum was also investigated, a report of which will be presented in the near future. It was interesting to note that the colostrum of nonimmunized and actively immunized mothers possessed very little antitoxin, and therefore, offered a very minor source of antibody transfer to the infant. This is best illustrated by some of the actively immunized mothers possessing an antitoxin titer of 50 to 100 units per cubic centimeter of serum, yet transferring to the infant only 0.1 unit or less of antitoxin per cubic centimeter by way of the colostrum. An article by Kuttner and Ratner bears out this finding.

As to the discomfort offered the patient with the doses of toxoid administered, it may be stated that the Schick-positive mothers complained very little of any reaction, whereas, occasionally, the Schick-negative mothers, receiving the routine dosage of toxoid, complained of painful arms and headaches.

The value of the Schick test as a stimulus for increased antitoxin formation in an already Schick-negative mother is illustrated by the following case: The mother of two children was Schick tested during the course of her third pregnancy, and the response was negative. I Schick tested the infant at nine months of age and also the two-year-old child who had not received any previous Schick test or immunization against diphtheria. The infant responded negatively to the test, whereas, the two-year-old child presented a definite positive reaction.

Whether the children of actively immunized pregnant mothers have been actively or passively immunized in utero is rather difficult to state, as at present, no method exists which differentiates active from passive immune bodies.

PITUITRIN SHOCK*

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IT IS imperative that untoward reactions following the use of a drug of established clinical value receive critical and precise scrutiny in order that such undesirable reactions may be avoided. A valuable therapeutic adjuvant might unnecessarily be discarded because of the fear of side effects which may be obviated or properly combated through a fuller appreciation of the pharmacologic actions and through a more intelligent usage of the offending drug.

These remarks, truisms applicable generally to all therapeutic agents, are pointed in this paper particularly to posterior pituitary preparations which have an accepted place in the armamentarium of obstetrics and gynecology chiefly, and to a lesser extent, in general surgery and internal medicine. The untoward reaction with which we are concerned primarily is that of "shock" appearing after the administration of a posterior pituitary preparation. "Pituitrin shock" is an infrequent but no longer rare experience as observed by a study of the literature. Its occurrence has received but passing mention in the standard textbooks on obstetrics and gynecology.¹

A review of the literature rewards one with isolated case reports. The earliest paper of interest is that of Hasson² who described a case of pituitary dysfunction being treated with posterior pituitary extract. After some period of repeated administration, the patient developed pruritus and angioneurotic edema following the injection of the preparation. While this case did not present evidence of shock, it is of interest because it served to describe pituitrin hypersensitivity which, in later re-

*Read at the Chicago Gynecological Society, November 15, 1940.

cent of adults are immune to diphtheria. Most of us accept that premise. That is why many say that it is impossible for a child under six months of age to have diphtheria, because it has been passively immunized by the mother.

Did the mothers who became Schick negative have small doses of toxoid? This question arises from an interesting parallel. There is available at the present time a tetanus toxoid which can be given to an individual in divided doses. If such a patient receives subsequently a contaminated wound, it is not necessary to administer tetanus antitoxin. Instead we can give the patient an injection of tetanus toxoid and immediately the titer rises. This is possible because the incubation period for tetanus is longer than that for diphtheria. It may be desirable to administer the combination toxoids to protect against diphtheria and tetanus.

Furthermore, it was significant that the highest blood titer level was obtained in the period between four and eight weeks. That bears out the work we are doing at the Municipal Contagious Disease Hospital. We administer to adults with positive Schick tests $\frac{1}{10}$ c.c. of toxoid intradermally. We observed in a large number of these patients that the Schick test became negative at the end of three weeks. The ordinary procedure is to give toxoid subcutaneously, at intervals of one month and hope to get a negative Schick in six months. I would like to ask whether this $\frac{1}{10}$ c.c. had been given through the skin. Perhaps the patients may have received what is equivalent to an intradermal dose of toxoid. This method is used in adults who would be made uncomfortable with subcutaneous injections. The systemic reactions are much less with $\frac{1}{10}$ c.c. intradermally.

We have used placenta extract in an endeavor to control an outbreak of measles. In our last epidemic of measles we used normal human serum in 40 c.c. doses, placenta extract in 2 c.c. doses, and in a third group convalescent measles serum in doses depending upon the age. The convalescent measles serum was more effective than pooled human serum. The placenta extract was of the least value. In the majority of instances we did not protect the child against a typical attack when placenta extract was used. At the Contagious Hospital, we desire to prevent the patient from developing measles.

The problem of whooping cough in infants under one year is of considerable magnitude. I wonder if the obstetricians might give the mother a little pertussis vaccine and save us some trouble.

DR. FREDERICK H. FALLS.—In 1924, working with colon bacillus pyelitis of pregnancy, we showed that immune bodies developed in the mother in response to the infection were transferred to the fetal blood, and that the titer of the agglutinins in the fetal blood was almost the same as the titer of the agglutinins in the mother's blood. Previous to that I had found that in asthma the substances which stimulate eosinophilia were transferred to fetal blood. Since then I have found eosinophilia in three other babies born to mothers with asthma. It is quite significant that these substances are manufactured by the mother and pass through the placenta into the fetal blood. In pyelitis, the causative organism is bound to get into the vagina in large numbers during labor. After rupture of the membranes these organisms will invade the uterus and placenta and secondarily infect the fetus. We would probably have fatal results in a large percentage of the cases were it not for the mobilization of protective agglutinins.

DR. LIEBLING (closing).—Dr. Black's question, whether the infant will be protected during the first six months of life following active immunization of the pregnant mother, may be answered in the affirmative. At present, I have followed a group of these infants beyond the sixth month of life and found that children born to actively immunized mothers presented a negative Schick test at the age of eight or nine months. Of greater interest is the transfer of passive immunity to the infant from a group of Schick-negative nonimmunized mothers. This may be attributed to the stimulating effect of the toxin in the Schick test material, as the offspring of this group of mothers also responded negatively to the test eight or nine months after birth. I, therefore, feel that Schick testing alone without active immunization of the mother has acted to protect the infant during the first nine months of life.

the pituitrin as the responsible agent. The negative skin tests, performed with the preparation used, rule out anaphylaxis as the cause of shock. Of interest is the unusual combination of shock and bradycardia which this case demonstrated. This bradycardia has been observed experimentally after the administration of pituitrin and may be due to vagal stimulation, direct myocardial action or intense coronary constriction.⁷

CASE 2.—F. B., aged 29 years, was admitted in labor to the obstetric ward service. Two years before admission the patient had been subjected to a cesarean section for an abruptio placentae. Because of a prolonged and unprogressive labor, the patient was brought to the operating room for delivery by section. Twenty minutes before the operation the patient was given $\frac{1}{50}$ gr. of atropine sulphate by hypodermic. Blood pressure at the start of operation was 120/90, pulse 76. The anesthetic agents used were ethylene and ether, administered by the closed, carbon dioxide absorption technique. At no time did the depth of anesthesia exceed that of first plane. A low cervical section was performed with the delivery of a living child. Immediately following delivery an ampoule of ergotrate was administered intramuscularly. Because of persistent poor uterine tone, 1 c.c. of obstetrical pituitrin was injected into the uterus; at this time the patient's blood pressure was 130/84 and pulse 100. Within five minutes the pulse rate rose to 120, while the blood pressure could not be obtained. The patient presented the picture of shock. For the following sixty minutes, the blood pressure could not be obtained. Ephedrine sulphate (gr. $\frac{3}{4}$) was given intramuscularly some thirty minutes after the appearance of shock with a resultant rise in pulse rate to 170-180 per minute with no effect on the arterial pressure. Pooled serum (500 c.c.) and 5 per cent glucose in saline (800 c.c.) were administered intravenously. Sixty minutes after the appearance of shock the systolic blood pressure could be obtained at 100, while the pulse rate fell to 140. The patient's recovery thereafter was rapid and uneventful. An intradermal skin test with obstetrical pituitrin (0.2 c.c. undiluted) resulted in the prompt appearance of a large urticarial wheal and a wide margin of erythema. On the fourth postoperative day the patient was given 500 c.c. of citrated blood because of profuse vaginal bleeding; this promptly produced a diffuse maculopapular eruption which was relieved with adrenalin.

Here, too, the absence of significant hemorrhage and surgical trauma and the almost immediate occurrence of shock on the injection of pituitrin point with certainty to the pituitrin as the responsible agent. The positive skin test and the maculopapular eruption following the transfusion indicate a state of allergy and suggest very strongly the possibility of anaphylaxis as the mechanism underlying the shock.

The remaining 5 cases of pituitrin shock occurred in women on whom vaginal hysterectomies were performed and who received intrauterine surgical pituitrin (1 to 2 c.c.) at the beginning of the operation. All recovered with no untoward effects. Of these 5 patients, only one was skin tested with pituitrin, and this one was found to be negative. These cases represent an incidence of 5 per cent of the total cases observed by the physician anesthetists.

MECHANISM OF PITUITRIN SHOCK

Various theories have been offered to explain the mechanism of pituitrin shock; these may be listed as (a) histamine reaction, (b) anaphylaxis, and (c) cardiac effect.

(a) In a discussion of our cases one may promptly dispose of the suggestion that histamine in the posterior pituitary preparation was the responsible agent, inasmuch as our solutions were histamine-free.⁸ This does not exclude histamine as a cause of shock in the use of earlier posterior pituitary preparations which were admittedly less pure than those of today.

ports, was found to be an etiologic factor in shock following pituitrin administration. Wang and Maxwell in 1933³ reported a case of anaphylaxis following the intramuscular injection of 1 c.c. of posterior pituitary extract in a patient during labor, as evidenced by intense pruritus, urticaria, and shock; recovery was effected by intravenous fluids and intravenous digitalis. This case is of particular interest because it raises the possibility of sensitization by previous administration of posterior pituitary preparations, as this patient had received such agents during her previous deliveries.

Since this report there have been several further cases⁴ described. These cases follow a somewhat similar pattern of events which may be described briefly as follows: the patient, in the second or third stage of labor, was given a hypodermic or intramuscular injection of a posterior pituitary preparation of a dosage varying from minims ii to 1 c.c.; within ten to thirty minutes angioneurotic edema, urticaria, dyspnea, and shock appeared. In a number of cases no shock appeared, with urticaria, pruritus, and angioneurotic edema as the major complaints. Adrenalin was found to be effective in relieving the symptoms in all cases. Those reports which included skin tests described their patients as sensitive to the extracts used; also, most of the cases revealed a history of some previous administration of the extract.

Not all reports are found in obstetric cases. Seed and others⁵ described a case of shock, in an elderly man with diverticulitis, following the injection of pituitrin; no skin tests were reported. Potter⁶ mentioned the occurrence of shock in 10 cases out of 1,200 who had received pituitrin for varying surgical conditions; no deaths occurred and all patients responded to fluids and adrenalin. No details were given.

Our experiences with pituitrin shock have been quite unique and undescribed, in that all our cases occurred while the patient was under surgical anesthesia. During the past year 7 cases have been observed demonstrating shock almost immediately after the injection of a posterior pituitary preparation (surgical and obstetrical pituitrin). These cases are reported to emphasize the danger of pituitrin shock and to discuss the mechanism of such reactions with a view toward careful and intelligent use of the drug and toward a rational therapy.

Of the 7 cases observed, 2 are herewith presented in some detail, being representative of our entire group.

CASE 1.—M. C., a 43-year-old white female, was admitted for a vaginal hysterectomy to the gynecology ward service. Her preoperative condition was good. On the operative morning, the patient was given $\frac{1}{6}$ gr. of morphine sulphate and $\frac{1}{150}$ gr. of scopolamine, one and a half hours before the scheduled time of operation. The anesthetic agents were ethylene and ether, administered by the closed, carbon dioxide absorption technique; at no time did the depth of anesthesia exceed that of first plane. Blood pressure at the start of the operation was 100/64, and pulse 90. Two minutes after the start of the operation, 1 c.c. of surgical pituitrin (20 pressor units) was injected intramuscularly in the arm in order to produce a less vascular operative field by virtue of its peripheral vasoconstrictor action. Within eight minutes the blood pressure could not be obtained; the pulse could be palpated with difficulty, being 60 per minute. The appearance of the patient was one of mild shock. During the remainder of the operation, a period of forty-five minutes, the blood pressure could not be obtained, while the pulse persisted between 48 and 54. Some forty-five minutes after the end of the operation, the blood pressure was found to be 110/70. Therapy consisted of 2,500 c.c. of 5 per cent glucose in saline intravenously. The patient's postoperative course was uneventful. Intradermal skin tests with surgical pituitrin (0.1 c.c. of undiluted and 1-10 dilution each) were negative.

The absence of significant hemorrhage and surgical trauma and the prompt appearance of shock following the administration of pituitrin point unequivocally to

similarity between the effects of anoxemia and of the injection of a posterior pituitary preparation on the heart. Goldenberg and Rothberger²⁰ stressed the similarity between the effects of pituitrin on the electrocardiogram and the electrocardiographic changes in angina pectoris and experimental coronary occlusion.

An anoxic heart will dilate; thus, Kolls and Geiling²¹ demonstrated by fluoroscopy and teleroentgenograms that pitressin produced dilatation of the heart. With a dilated, anoxic heart, there will result a reduction in cardiac output even to zero, with a resultant fall in blood pressure to an extent that will depend upon the degree and duration of the myocardial anoxia. The mechanism of pituitrin shock when not due to anaphylaxis is briefly as follows: coronary constriction, myocardial anoxia, dilatation of the heart, decrease in cardiac output, fall in blood pressure.

The role of the anesthetic agent in pituitrin shock is an uncertain and speculative one.

The most significant studies in this problem are those of Melville²² who observed that dogs under sodium phenobarbital anesthesia were peculiarly sensitive to posterior pituitary extract as evidenced by the occurrence of ventricular fibrillation and death. Melville concluded that the coronary constriction in the phenobarbitalized dog was greater than in the unanesthetized dog and that this drug exerted some depressant action on the myocardium. From the work of Cattell,²³ it would appear that ether will enhance the action of pituitrin on the heart. He demonstrated an increase in heart volume during inhalation of ether, the heart volume steadily increasing with deepening anesthesia. In addition, Cattell showed that ether has a depressing effect on the blood pressure in shock, perhaps due to some disturbance in the vasoconstrictor system.

It is interesting to speculate that the inhibition in tissue oxidation under narcotics and anesthesia²⁴ is a factor that sensitizes the heart under anesthesia to the deleterious effects of pituitrin.

THERAPY

The treatment of pituitrin shock in the unanesthetized individual whether due to anaphylaxis or to coronary constriction, is the same: intravenous fluids, preferably blood or serum, oxygen and adrenalin or ephedrine. The use of adrenalin and ephedrine in anaphylaxis need not be expanded upon. However, it is well to point out the rationale of the use of these drugs in pituitrin shock due to coronary constriction. Melville and Stehle¹⁵ have shown adrenalin and ephedrine to be effective antagonists of pituitrin by virtue of their dilating action on the coronary arteries.

In the anesthetized patient, the problem of therapy is less simple since the anesthetic agent may sensitize the heart to adrenalin and ephedrine, so that the use of either drug might prove catastrophic to the patient. Thus, Meek and co-workers²⁵ have shown that cyclopropane has a marked sensitizing effect upon the cardiac automatic tissues so that adrenalin may produce ventricular tachycardia or ventricular fibrillation; adrenalin is contraindicated in cyclopropane anesthesia. These same workers also found that adrenalin produced fast nodal tachycardias under ether anesthesia, an undesirable burden in an already anoxic heart in shock.

Orth and co-workers²⁶ found that cyclopropane and ether sensitized the sinoauricular node with the result that ephedrine will produce

(b) That anaphylaxis may well reproduce the clinical pictures described is unquestioned. Most of the cases examined in the literature revealed, in addition to shock, the clinical features of urticaria, pruritus and angioneurotic edema. Where skin tests were performed, all revealed sensitivity to the posterior pituitary preparation. Many cases presented a history of having received a posterior pituitary preparation on some previous occasion. The studies of Simon and Ryder⁹ would indicate that the responsible antigen was not the oxytocic or vasopressor fraction, but rather some other constituent of the gland. In this paper it will suffice to emphasize the possibility of pituitrin anaphylaxis.

(c) Of more interest to us are the cardiovascular effects of pituitrin, effects which have received too little attention by the clinician and merit some detailed discussion. It would appear paradoxical that a posterior pituitary preparation containing a pressor substance (pitressin), should produce shock by some mechanism other than anaphylaxis; however, the physiologic explanation is not lacking.

It is commonly held that the injection of a posterior pituitary preparation results in a rise in arterial pressure, but this is erroneous.

Moffat¹⁰ found insignificant blood pressure changes in the unanesthetized patient following intramuscular administration of pituitrin. Woodbury and co-workers¹¹ observed transient falls in arterial pressure in anesthetized and unanesthetized patients following the intravenous and intrauterine administration of surgical and obstetric pituitrin; these falls were in the range of 30 to 50 mm. Hg. They also showed that the intravenous administration of three units pitressin produced very small rises in blood pressure.

Our own observations in anesthetized patients indicate that the intra-uterine and intramuscular administration of surgical and obstetrical pituitrin are followed by variable results; there is usually no appreciable change, and infrequently, a significant rise or fall in arterial pressure.

In the experimental animal, the effects of pituitary preparations on blood pressure have been varied.

Gruber¹² demonstrated that pitressin in the unanesthetized dog produced a fall in arterial pressure when given intravenously; pitocin gave variable results while pituitrin produced a rise in pressure. These findings were confirmed by Melville.¹³ In the anesthetized animal, Raginsky¹⁴ obtained results dependent upon the anesthetic agent used; thus, with chlorotone, pituitary extract produced almost constantly a rise in blood pressure; with ether the results were of a pressor, depressor, or mixed type; with luminal the effect was pronouncedly one of a depressor type. It is generally agreed that the pressor response to pituitrin is due to arteriolar and capillary constriction. The explanation for the fall in blood pressure is to be sought elsewhere in the cardiovascular system; here our attention is brought to the action of pituitrin upon the heart and coronary vessels.

It has been shown by Melville and Stehle¹⁵ that the pitressin fraction possesses a potent constrictor effect upon the coronary arteries; this has been confirmed by Visscher¹⁶ and Katz and co-workers.¹⁷ Such coronary constriction leads to anoxia of the myocardium to a degree that will vary with the intensity and duration of the constriction. Grollman¹⁸ suggests that pituitrin per se may interfere with the oxidative processes of the heart and thus augment the anoxic action of coronary constriction. It is of interest to note that Resnik and Geiling¹⁹ point out the

The use of pituitrin in patients with evidence of coronary insufficiency should be interdicted.³⁰ One of our patients was a middle-aged colored female with syphilitic heart disease. Surgical pituitrin (1 c.c.) was injected into the uterus against the advice of the medical anesthetist, with the prompt appearance of shock. Recovery was uneventful.

Finally, when the use of pituitrin is essential, care must be taken that it is not given intravenously—this by a simple aspiration test in two planes before injecting.

As for the physician anesthetist, it is not sufficient that he merely knows that pituitrin shock may occur under anesthesia. It is within his province to warn the surgeon of the effects of pituitrin and to express an opinion as to the advisability of its use. The administration of pituitrin during anesthesia should be guided by the anesthetist whenever possible, to insure that the preparation is not given intravenously. When pituitrin shock does occur under anesthesia, the course of therapy should be guided by the physician anesthetist who is in a position to judge best the behavior and state of the patient and the response to the various therapeutic procedures.

SUMMARY

1. Seven cases of pituitrin shock occurring under anesthesia are reported, two in detail. A brief review of the pertinent literature is presented.

2. Pituitrin shock may be a manifestation of (a) anaphylaxis, frequently due to previous sensitization with a posterior pituitary preparation, or (b) coronary artery constriction with resulting myocardial anoxia, cardiac dilatation, and decreased cardiac output.

3. Therapy in the unanesthetized patient, whether due to anaphylaxis or coronary constriction, should consist of adrenalin (or ephedrine), intravenous fluid, and oxygen. In the patient anesthetized with ether or cyclopropane, adrenalin (or ephedrine) might prove deleterious to the patient, and therapy should be confined to the use of intravenous fluid and oxygen.

4. Modes of usage of pituitrin are discussed with a view toward elimination of shock reaction.

The authors are indebted to Dr. Ralph Reis and Dr. Irving Stein for the privilege of reporting their cases.

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greatly increased sinoauricular rates. In retrospect, the use of ephedrine in our second case of pituitrin shock, with a rise in ventricular rate from 120 to 180, probably demonstrated the production of an increased sinoauricular rhythm during ether anesthesia.

Orth and co-workers also observed that neosynephrin could be used safely under ether and cyclopropane anesthesia as an analeptic; if available, neosynephrin may therefore be used in conjunction with intravenous fluids and as much oxygen as maintenance of anesthesia permits.

There is no contraindication to the use of adrenalin or ephedrine under ethylene or nitrous oxide anesthesia.

DISCUSSION

The cases herein reported and those found in the literature serve well to indicate that pituitrin shock is no rare occurrence, and it is safe to say that its frequency is far greater than suspected and reported. Little consolation can be found because of the absence of case reports of deaths following the use of posterior pituitary extracts; too often such catastrophes are treated with complete silence.

It is the problem of the surgeon and the physician anesthetist to reduce the incidence of pituitrin shock to a minimum. The surgeon may help attain this end, first, by appreciating the pharmacologic effects of posterior pituitary extracts, and second, by defining clearly the indications for and the mode of use of such preparations. We have emphasized the former; some attention may well be paid the latter.

The use of pituitrin (intrauterine or intramuscular) to diminish bleeding during a vaginal or abdominal hysterectomy is a poor and dangerous substitute for careful and scrupulous hemostasis; the possibility of an intrauterine injection being made into a vein is great. Similarly, the intrauterine administration of pituitrin during a cesarean section is hazardous in view of the great vascularity of a gravid uterus. Where an oxytocic agent is needed, it would be more discrete to use an ergot preparation or pitocin which has no constrictor action on the coronary arteries. In addition, the obstetrician should be aware of the fact that sensitization to posterior pituitary preparations from previous administrations is not rare and should be alert to the possibility of an anaphylactic reaction.

When repeated injections of pituitrin are contemplated, as in postoperative abdominal distention, conservative doses should be the rule, averaging 10 to 20 pressor units for the individual dose; at this point reference may be made to a paper by Chaikoff²⁷ who advises that when pituitrin (or pitressin) is used in postoperative abdominal distention, it be combined with ephedrine, the latter in order to neutralize the coronary constriction of pituitrin.

The use of pituitrin as an analeptic in spinal anesthesia and shock is unsafe, carrying as it does the danger of coronary constriction; however, it may be effectively and safely used for such purposes when combined with ephedrine. This combination has been suggested by Melville²⁸ and its value confirmed by Hand and Sise²⁹ and Chaikoff.²⁷

CANCER OF THE CERVIX FOLLOWING SUPRAVAGINAL HYSTERECTOMY*

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THERE is still a difference of opinion as to the advisability of doing a total hysterectomy in all cases if the uterus is to be removed as a prophylactic measure against a possible carcinoma developing in a retained cervix. In 1934 Von Graff wrote an article advocating that total hysterectomy should be done routinely. Since then several authorities have taken the opposite view in their discussions.

All will agree that the total operation offers the best protection from cancer, although cancer of the cicatrix in the vaginal vault occasionally occurs. Tyler has reported 13 cases of cancer of the vaginal vault following the total operation, and Rouhier reported an epithelioma of the cicatrix in the vaginal vault twenty-six years after total hysterectomy.

In these cases there naturally arises the question as to whether some portion of the cervix was left unintentionally, or was it a primary carcinoma of the vagina.

The technique employed in the complete operation should preserve the supporting structures of the upper pelvic floor. The technique described by Worrall of Australia and that of Lahey of Boston, if properly done, includes the entire portio vaginalis and is not difficult. In my experience it has been most satisfactory. Richardson and Farrar have also described efficient techniques.

However, many surgeons believe that there is a definite increase in the postoperative mortality and morbidity in the total operation as compared to the subtotal, and that the incidence of stump cancer is less than the increase in mortality percentage, especially where there is no disease or injury of the cervix. There is also a difference of opinion as to the cure rate obtainable in these stump cases. Prominent authorities have argued both sides of these questions.

In 1896 Chrobak first described, as a clinical entity, carcinoma of the stump of the cervix left after subtotal hysterectomy. Polak in 1921 collected 256 cases from the literature which awakened interest in the subject, and numerous reports of this condition continue to appear, especially during the last decade.

The incidence of stump cancer is difficult to determine and varies greatly in different reports. Von Graff found in one compilation of 7,244 subtotal hysterectomies there was an incidence of 45 stump cancers, or 0.62 per cent, while in his report of the number of stump cases found in a series of carcinoma of the cervix from different cancer clinics, there were 176 in 4,269, or 4.1 per cent. This is an approximate average percentage, although some clinics have a much higher incidence. In 1933 we reported 40 cases in 558, or 7.2 per cent.

Formerly 0.6 per cent was considered the probable incidence, while today 4 per cent is six and one-half times greater, and the real frequency may be still larger. The difficulty in determining the incidence

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DISCUSSION

DR. HAROLD O. JONES.—We have used pituitrin, usually 1 c.c. of surgical, in many plastic vaginal operations as well as abdominal procedures. We have not appreciated many of the mild reactions as due to pituitrin but have interpreted them in terms of the surgical procedures performed.

Pituitrin has been of distinct value in reducing the blood loss during vaginal hysterectomy, and in our experience has not resulted in any instances of late hemorrhage.

In the patients under my own observation, we have had only one with appreciable "shock" quite certainly due to pituitrin. This patient was sent to the operating room for a diagnostic curettage on account of uterine bleeding; no anesthetic agent was administered, as it was found that the cervix was so patulous that dilatation was not necessary. Curettage was carried out and rather free bleeding followed. One cubic centimeter of surgical pituitrin was injected into the tissues at the side of the cervix; care was taken to be sure that the needle did not enter a vein. The patient returned to the ward in good condition and a few minutes later was in very profound shock, pulseless, cold and clammy, blood pressure 60/—, respirations 8 per minute. Intravenous fluids, ephedrine, oxygen caused some response, but not until twelve hours later did we feel safe about this patient. This patient recovered without any detectable residues. We did not test out her sensitivity to pituitrin later.

insertion of the radium capsule is a great help in some cases. In our cases we place a radium capsule in the cavity of the cervix, 50 or 100 mg., and implant platinum needles, $12\frac{1}{2}$ mg., 4 to 6, in the periphery according to the size of the cervix, giving an average dose of 3,200 to 3,600 mg. hours, which may be divided as indicated. This is either preceded or followed by high voltage x-ray therapy, preferably by the Coutard technique. Fricke of the Mayo Clinic gives up to 4,000 mg. hours in 3 or 4 divided doses, plus x-ray.

The opinion as to whether the total removal has a higher mortality rate than the subtotal operation varies in accordance with the experience of the surgeon. Many only remove the cervix when it is easy to do. The skilled operator will no doubt have less difficulty than the occasional surgeon. There is no question, however, that some cases, are extremely difficult for any surgeon on account of obesity, adhesions, and fixation of the uterus. The total removal in such cases is a more severe procedure, no matter who does it or by what technique, and the mortality and morbidity will average higher.

In my opinion, in view of the rate of incidence as we see it, and the more frequent association of carcinoma with fibroma, it is best to remove the entire uterus in all cases where there is no probability of serious increased risk. If the cervix is retained on this account, it should be coagulated or repaired when indicated, and meticulously watched in a careful follow-up over an extended period of time. Whenever a hysterectomy is contemplated, the cervix should always be carefully studied, and if suspicious a biopsy should be made.

It is important that the uteri removed be opened and inspected at the time of operation, and if the cervix is suspicious it should be removed in spite of an increased risk.

RESULTS

Healy and Arneson in 1935 published their results obtained in treating stump cancer, and their five-year salvage was 14 per cent. They attributed their poor salvage to the anatomic difficulties and change caused by the absence of the fundus, as it did not allow of the same perfect application of the radium, or the same degree of dosage. The 14 per cent was lower than their salvage percentage of all their cancer cases. They state, however, that their results in the advanced cases of stump cancer equaled their results in advanced cancer with the uterus present. They evidently rely more on the external radiation with x-ray, advising the Coutard technique.

On the other hand, Behney has reported a 10 per cent better percentage in his stump cases than in his total series; and Scheffey's salvage was 42.8 per cent against 20.5 per cent for his total cases.

The last report from the Woman's Hospital on carcinoma of the stump was published three years ago when Dr. Sackett found an incidence of 7.2 per cent. This report included all cases, even though they occurred within the first year following hysterectomy. I have recently had the records brought up to date, from May, 1919, to November, 1940. This shows that in 879 patients with carcinoma of the cervix there were 61 stump cases, or 6.9 per cent. In 49 observed during a five-year period, 21 were living, or an absolute survival rate of 42.8 per cent; and in 20 observed during a ten-year period, 10, or 50 per cent, were living. Our five-year salvage of all cancer of the cervix cases was 28.5 per cent. In the 61 cases, 16 were within the first year after operation. Of these, 5 survived five years and 3 ten years. Undoubtedly the disease was already present in some of this group at the time of the hysterectomy.

is due to the uncertainty of the presence of carcinoma at the time of the subtotal operation. It is fair to presume that the carcinoma was already present if it appears within the first year after the subtotal hysterectomy.

Pearce of Boston stresses the slow development of carcinoma in some cases, mentioning as long as four years after its onset. Nuttall and Todd suggest a two-year criterion; Healy believes a three-year period should elapse as a fair index, to which Behney agrees.

It is important to note that there is a coincidence of fibroids and cancer in the same uterus.

Herbert Spencer, in 1902, was the first to recognize the frequent coincidence of malignant disease with fibroids. He found 4 cases of cancer in 200 fibroid uteri. Schottlaender found 12 in 600, and Noble found 2 in 100 cases, or a total series of 18 cancers in 900 fibroids, or 2 per cent. Labey, in 1924, before the French Congress of Surgery, stressed the frequent association of fibroma and cancer as proved by total hysterectomy. Piquand found in 600 uteri without fibroids 4 cases of cancer and in 600 cases with fibroids 21 cases of cancer. As most hysterectomies are done for fibroids, this is an important factor to consider in choosing the type of operation.

Spencer, Masson, Von Graff, Lynch, Sampson, Farrar, and many others advocate routine total hysterectomy as a prophylactic measure against stump cancer, believing that there is very little added risk in skilled hands.

Healy states the low incidence does not justify the total operation on account of increased mortality.

Scheffey, Behney and Meigs, among others, do not advocate the total operation in every case, reserving it for those in which the cervix is badly diseased. In the milder cases they advocate appropriate preliminary treatment, such as cauterization or repair.

Some surgeons rely on coning out the mucosa of the cervix, or cauterizing, or carbolicizing its cavity as a preventive of malignancy. This is no safeguard, as 80 per cent of cancers originate on the portio vaginalis.

Sidall and Mack showed that in average hands the mortality of the total operation is higher than the subtotal. In 4,559 total operations, it was 3 per cent, and in 7,795 subtotal, it was 2.6 per cent.

Richardson expects the mortality in either operation should not exceed 1.5 per cent in skilled hands, but points out that in the total operation the morbidity and complications are greater, and that it is not the average operator alone who finds it more difficult.

Hochman, a student of mine, studied, under my supervision, 1,114 cases of total and subtotal hysterectomies and reached the conclusion that in the hands of the average operator there is a definite increased operative risk accompanying the complete operation.

In my experience, the incidence of vesicovaginal fistula is higher in stump carcinoma, probably due to the effect of the radium or the carcinoma on the bladder, which is in close approximation to the top of the stump. I have found it one and one-half times higher in these cases. Behney found fistula three times as often in treated and untreated stump cases of his series. Consequently, I believe it is wiser and safer to give divided doses of radium rather than one large dose.

The difficulty in applying the radium varies according to the extent of the disease and the shape and size of the cervix. Behney's method of splitting the cervix transversely with the radioknife to allow of the

SOME CLINICAL OBSERVATIONS ON THE ENDOCRINOLOGY OF ABORTION*

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THE etiology of abortion is varied. When no medical or gynecologic cause is apparent, it has been common practice to look for some disturbance in the endocrine system or to take ultimate refuge in some theory of glandular failure. At times, clear-cut factual data are available to establish the endocrinopathy of abortion. The high incidence of abortion in hypothyroid women and the specific therapeutic efficacy of thyroid substance are well known. Abortion is a common complication of pregnancy in diabetic women, the incidence of which has not been altered significantly by adequate therapy with insulin and diet. Myopathic insufficiency of hypoplastic uteri, resulting from embryologic faults or from adolescent ovarian failure, may cause abortion. The most common theory employed to explain repeated abortions, when no organic or traumatic factors exist, is based on an assumed intercurrent ovarian or placental failure. This communication deals with some clinical observations pertinent to this theory.

A time-honored concept of the physiology of corpus luteum attributes to it the role of protecting and nurturing the product of conception. Its active principle, progesterin, has been described as exerting a quieting and relaxing action upon uterine musculature. Accepted as generally as it is in experimental biology, this concept has both its ardent proponents and opponents in clinical endocrine gynecology. Falls and his co-workers¹ regard progesterone as a quantitative, biologic antidote to pituitary oxytocin, endogenous and exogenous. Kurzrok and his associates,² on the other hand, have observed increased uterine contractility following injections of progesterone.

Further considerations indicate that, despite the fundamental role attributed to it in the physiology of pregnancy, the corpus luteum at times is not indispensable to the normal progress of gestation. Pratt³ reported in 1927 the nonoccurrence of any interference with the course of pregnancy or lactation in the instances of 2 women whose corpora lutea were removed during the first month of pregnancy, in fact prior to the first missed period. Such observations may even cast doubt upon the absolute necessity for the corpus luteum in implantation of the fertilized ovum. Ask-Upmark⁴ reviewed the records of 51 women from whom the corpora lutea were removed during the first two months of pregnancy. Pregnancies continued in 9 of these women, despite the fact that in 4 instances corpora lutea had been removed during the first

*Read, by invitation, at the Detroit meeting of the Michigan Society of Obstetricians and Gynecologists, October 1, 1940.

In 41 the disease developed more than one year after operation. Sixteen of this group survived five years, or 32.7 per cent of 49 observed, and 7 survived ten years, or 35 per cent of 20 observed.

There were 32 cases arising three years following operation, or 3.64 per cent, which approaches the 4 per cent of average incidence in which the carcinoma was not present at the time of hysterectomy.

In the 61 cases, the extent of the disease was classed as early in 16 and advanced in 45. Forty-seven cases were squamous cell carcinoma, of which 20, or 44 per cent, survived five years, and 9, or 20 per cent, survived ten years. There were 12 patients with adenocarcinoma, 2, or 20 per cent, surviving five years, and 1, or 10 per cent, ten years. In 2 cases the type of cell was undefined. The incidence of fistula was one and one-half times as high in our stump cases.

The average dose of radium applied was approximately 3,200 mg. hours of element. High voltage x-ray follows, or precedes, preferably after the Coutard technique. Before 1930 we had no high voltage x-ray. Thirty-six patients were treated with radium alone (of these 29 were under treatment before 1930), 16 of these survived five years, and 9 survived ten years. Twenty-four patients were treated with both radium and x-ray; of these, 5 survived five years and 1 survived ten years. One patient was not treated.

As Behney has pointed out, the salvage of stump cases for five years in Scheffey's, Behney's, and our Clinic, if combined, was approximately twice that achieved with general carcinoma of the cervix in the same Clinics.

COMMENT

The general impression has been that cancer of the stump is more serious and more difficult to treat, with less hope of success than cancer of the cervix with the fundus present. With the exception of the increased frequency of fistula, which may be due to the carcinoma as well as the radium, in view of our results and those obtained by Scheffey, Behney, and others, I do not believe the above statement is justified. I agree with Behney's statement in a recent paper before the American Gynecological Society that stump cancer behaves and responds to treatment in a manner similar to cases where no operation has been done, with generally better results. If castration is combined with the subtotal hysterectomy, it should be expected to be a retarding factor in the cancer development due to diminished circulation and lymphatic drainage.

In my opinion the total operation is to be preferred and is my present practice, because of the evident higher incidence of stump cancer than was formerly thought to occur, and of the frequent association of cancer with fibroids. Yet we must recognize that in average hands there is more danger of a higher mortality, and such complications as injury to the bladder and ureters, infection, and lack of vaginal support than in skilled hands. Also the expert surgeon will meet cases with a definite increase in risk due to obesity, adhesions, fixation, or systemic disease, which makes the subtotal operation a safer and wiser procedure. If, however, the subtotal operation is considered, a careful study of the cervix should be made and appropriate treatment used if indicated.

In all subtotal operations, the possibility of cancer should be borne in mind, and a careful follow-up for an extended period of time is essential for safety.

of studies upon pregnanediol titers in health and disease has appeared. Stover and Pratt¹⁵ observed no significant alteration in pregnanediol titers of 3 individuals who had signs and symptoms of threatened abortion (1 gave a history of repeated abortion). Buxton¹⁶ recently reported the occurrence of normal titers of sodium pregnanediol glucuronide in the early pregnancies of 5 women, each of whom had 3 or more spontaneous abortions. Pratt and Stover and our group¹⁷ reported simultaneously that injections of progestin or progesterone failed to increase pregnanediol titers of patients receiving this type of therapy. Further studies by our group¹⁸ on the metabolism and utilization of crystalline progesterone continue to confirm these observations. It was found that quite large quantities of progesterone could be given without any pregnanediol being recovered from the urine. We also reported data which indicated that the injection of crystalline progesterone tended to inhibit the metabolism of the intrinsic progestin, i.e., pregnanediol titers were actually decreased by injections of progesterone. It was observed in these studies, however, that the concomitant administration of estrogens and progesterone tended to prevent this depression and at times resulted in some increase in pregnanediol titers. The simultaneous administrations of chorionic gonadotropins, progesterone, and estrogens yielded our only definite increases in pregnanediol titers. These observations seemed to cast considerable doubt upon the therapeutic specificity of progesterone in the treatment of threatened or habitual abortion, even in those instances in which low pregnanediol titers were associated. The theory of Browne and Venning that one might be able to establish quantitatively the progestin deficits by their method and to complement these deficits by progesterone therapy seems untenable.

CLINICAL DATA AND CASE REPORTS

The case records of 6 women who either had had repeated abortions or who were threatening to abort are reported. These patients were investigated both from an endocrine and a gynecologic standpoint. All had repeated daily determinations of pregnanediol by Venning's method. A number had daily determinations of 17-ketosteroids (products of androgenic metabolism) by Oesting's method.¹⁹ All of these patients except one were treated with progesterone alone or with progesterone and estrogens, or progesterone and chorionic gonadotropins.

CASE 1.—Abortion at 6 months. No treatment except thyroid substance. A. B., colored, aged 35 years, married, para 9-9-0, was seen in the Endocrine Division Sept. 21, 1939, at which time she was approximately four months pregnant. All of her nine previous pregnancies had ended in miscarriages at five to six months of gestation. Endocrine and gynecologic surveys indicated no apparent abnormalities or disease except generalized obesity (weight 183 pounds). Roentgenogram of the sella turcica was normal. Basal metabolic rate was reported to be -20 per cent. The urinary excretion of sodium pregnanediol glucuronide was investigated from Sept. 22 to Nov. 6, 1939, i.e., to within five days of the time the patient miscarried.

These findings are presented graphically in Fig. 1. No treatment was given except thyroid substance to clinical tolerance.

The patient is now (Sept. 25, 1940) about five and one-half months pregnant and has been receiving anhydrohydroxyprogesterone,* 60 mg. a day, and thyroid substance to tolerance since the second month of pregnancy.

The abortion of this patient occurred at about the sixth month just as her previous 9 abortions. The pregnanediol titers were quite normal and compatible with the stage of gestation until a distinct fall in these occurred about a week before abortion. By referring to these titers, impending abortion could not have been diagnosed until the week before it actually occurred, and any treatment which had been anticipated upon the basis of low pregnanediol titers would not have been initiated until that time.

*Pranone, supplied generously by Schering Corporation, Bloomfield, N. J.

month of pregnancy. On the other hand, there is a mass of surgical data which indicate that trauma to, or removal of, the corpus luteum in the early months of pregnancy commonly results in abortion. There is, however, general acceptance of the belief that corpora lutea or even both ovaries may be sacrificed during the later stages of pregnancy with no untoward sequelae as regards the course of pregnancy. Explanation of this dispensability of the corpus luteum rests upon the assumption that its endocrine functions are taken over by the chorioplacental system.

A definite division of labor, as regards endocrine function, between the ovaries and the chorioplacental system has been envisioned by Browne and Venning.⁵

They divide pregnancy into ovarian and chorioplacental phases. During the ovarian phase the urinary excretory values of estrogens and of the pregnanediol complex are low, while those of the gonadotropins are high. During the chorioplacental phase these values of estrogens and pregnanediol complex increase, while those of gonadotropins decrease. The time of transfer of endocrine responsibility from the ovaries to the chorioplacental system is said to vary markedly and to be indicated roughly by a peak in the urinary excretion of gonadotropins. This theory assumes that an early transfer of responsibility to the chorioplacental system may permit early sacrifice of the ovaries. In such striking instances of dispensability of the corpus luteum as reported by Pratt, one may assume that an essentially normal progesterational endometrium may be capable of supplying the hormonal requirements for the continuation of pregnancy.

There is an abundance of data to confirm the belief that the chorioplacental system is a source of the hormonal plethora of pregnancy.

Allan and Dodds⁶ summarized 4 histories of patients reported by Amati, Szarka, Waldstein, and Saidl and added one patient of their own in whom pregnancy continued despite bilateral oophorectomies. They observed in the records of these patients no significant alterations in the urinary excretory values of gonadotropins, but they did observe definite decreases but no absences of estrogens. Venning and Browne observed no significant alterations in the urinary excretion of estrogens and of pregnanediol complex in a patient in whom pregnancy continued despite the removal of the corpus luteum on approximately the ninetieth day of pregnancy.

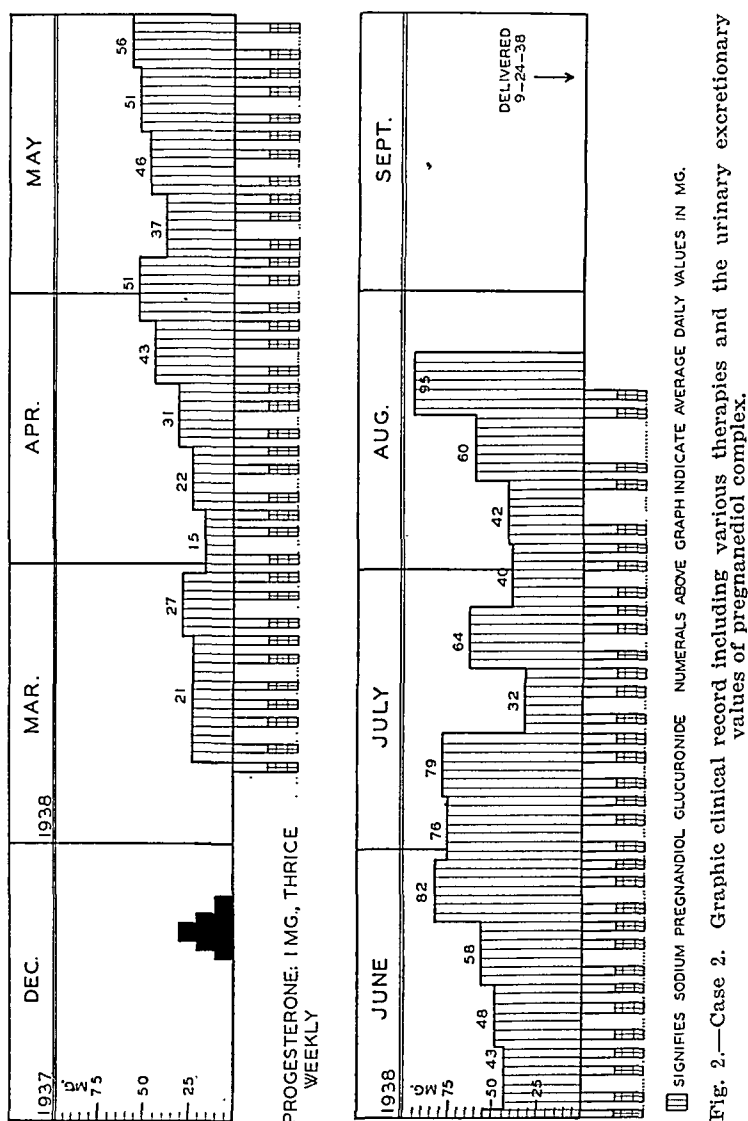
Studies of functional levels of corpus luteum activity in abortion as well as in other conditions related to ovarian failure have been hampered by the fact that biologically active progesterin either does not occur or occurs in small quantities in the various fluids and tissues of the body.

Only small amounts of progesterin were found by Adler and co-workers⁷ and by Ehrhardt⁸ in human placentas and in the urines of pregnant women. Loewe and Voss⁹ found only 1 rabbit unit of biologically active progesterin in 20 liters of urine from women during the last five days of the menstrual cycle. Bloch¹⁰ reported that 500 c.c. of blood from a pregnant woman gave negative results when tested by methods of bio-assay. Claiberg and his associates¹¹ obtained only a questionable progesterational reaction with an extract prepared from approximately 50 Gm. of human corpora lutea. Pratt and his co-workers,¹² however, were able to get positive tests in the immature rabbit with extracts equivalent to 60 Gm. of human corpora lutea. Our group¹³ has shown that even after injections of rather large amounts of progesterone or after the ingestion of rather large doses of anhydrohydroxyprogesterone no biologically active progesterin may be recovered from the urine.

Venning and Browne, however, in their various studies have been able to adapt Venning's method for the gravimetric determination of sodium pregnanediol glucuronide¹⁴ to the study of progesterin metabolism. They have submitted data to prove that pregnanediol is the major metabolic product of progesterin. A number

critical depressions of these titers. The patient's therapy was continued through the eighth month of pregnancy. Whatever the cause of the patient's threatened abortion, it was not related to any depression in pregnanediol titers.

CASE 4.—Abortion at five and one-half months occurring in a patient who had had 3 previous abortions. Treatment with estriol glucuronide, progesterone, and chorionic gonadotropins. Mrs. R. M., aged 30 years, para 2-2-0, was seen first in the Endocrine Division Sept. 22, 1939, at which time she was in the process of having a six weeks' abortion. The patient aborted despite progesterone therapy three days later.



The patient's two previous pregnancies had been aborted at about six weeks of gestation. General endocrine and gynecologic surveys showed no abnormalities. Basal metabolism was reported as -20 per cent.

Fig. 4 outlines the clinical course of the patient from the time of her third abortion through the beginning of her fourth pregnancy and until her fourth abortion. The patient received progesterone, estriol glucuronide, and chorionic gonadotropins as indicated in the clinical chart, as well as thyroid substance to tolerance.

The normal pregnanediol titers of this patient led to the hope that pregnancy would be carried to term. These titers during the three months they were investigated

CASE 2.—Pregnancy successfully carried to term in a woman who had had 3 previous abortions. Treatment with progesterone and thyroid substance. Mrs. A. H., aged 26 years, para 3-3-0, was seen first in the Endocrine Division March 9, 1938, at which time she was about two and one-half months advanced in her fourth pregnancy. Her three previous pregnancies had been aborted spontaneously at about the third month. Gynecologic and endocrine surveys showed no evidence of endocrine disease, except symmetrical obesity and clinical hypothyroidism. A basal metabolic test done just prior to the beginning of pregnancy was reported as -21 per cent. This finding had resulted in the administration of thyroid substance to clinical tolerance throughout the course of the patient's pregnancy.

Fig. 2 indicates the course of this patient during her pregnancy up until delivery of a healthy child Sept. 24, 1938. During the pregnancy the patient received progesterone as indicated in the clinical chart and excreted rather normal amounts of sodium pregnanediol glucuronide.

One is inclined to attribute the successful outcome of this pregnancy to the thyroid substance given and to restricted activity rather than to the small dosage of progesterone, i.e., 1 mg. three times a week. Throughout pregnancy the patient's pregnanediol titers were essentially normal. The amount of progesterone given could not have maintained normal levels of pregnanediol excretion had these been significantly low initially. The patient's pregnancy was complicated by a moderate toxemia during the last month. The albuminuria during this time interfered with pregnanediol determinations which otherwise would have been continued until the onset of labor.

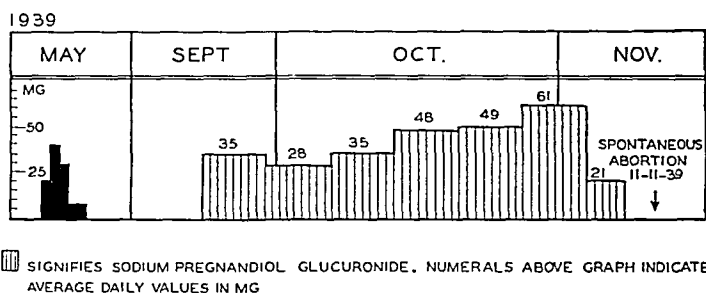


Fig. 1.—Case 1. Graphic clinical record, including urinary excretory values of pregnanediol complex.

CASE 3.—Pregnancy following gonadotropic therapy in a patient with ovarian sterility. Threatened abortion during the third month of pregnancy, despite initiation of therapy with estriol glucuronide, progesterone, and chorionic gonadotropins as soon as pregnancy was diagnosed. Eventual delivery at term. Mrs. M. McC., aged 25 years, para 0-0-0, was seen in the Endocrine Division July 11, 1939, because of inability to conceive during her five and one-half years of marriage. She had received no endocrine investigation or therapy. Her last sterility investigation had embraced a tubal insufflation about two and one-half years previously. Despite the fact that she gave a history of marked oligomenorrhea since menarche at 15 until approximately one and one-half years previously, endocrine and gynecologic surveys were essentially normal. Roentgenogram of the skull was negative. Basal metabolism was -12 per cent.

The endocrine investigation of this patient, as well as the patient's therapy which resulted in pregnancy, and the course of this pregnancy, which was threatened by abortion, are given in Fig. 3.

The interest in this case lies in the fact that for an entire month this patient threatened to abort despite bed rest and despite prophylactic therapy designed to prevent possible abortion started when pregnancy was diagnosed. The patient bled so profusely during her threatened abortion that her obstetrician felt sure that she had aborted. Despite these symptoms of threatened abortion pregnanediol titers were increasing steadily and normally, and at no time were there observed any

logic and endocrine surveys indicated no significant disease. Basal metabolic rate was reported as +10 per cent, satisfactory. Roentgenogram of the sella turcica was normal. The details of the investigative studies done and of the patient's therapy during the course of her pregnancy are given in Fig. 5.

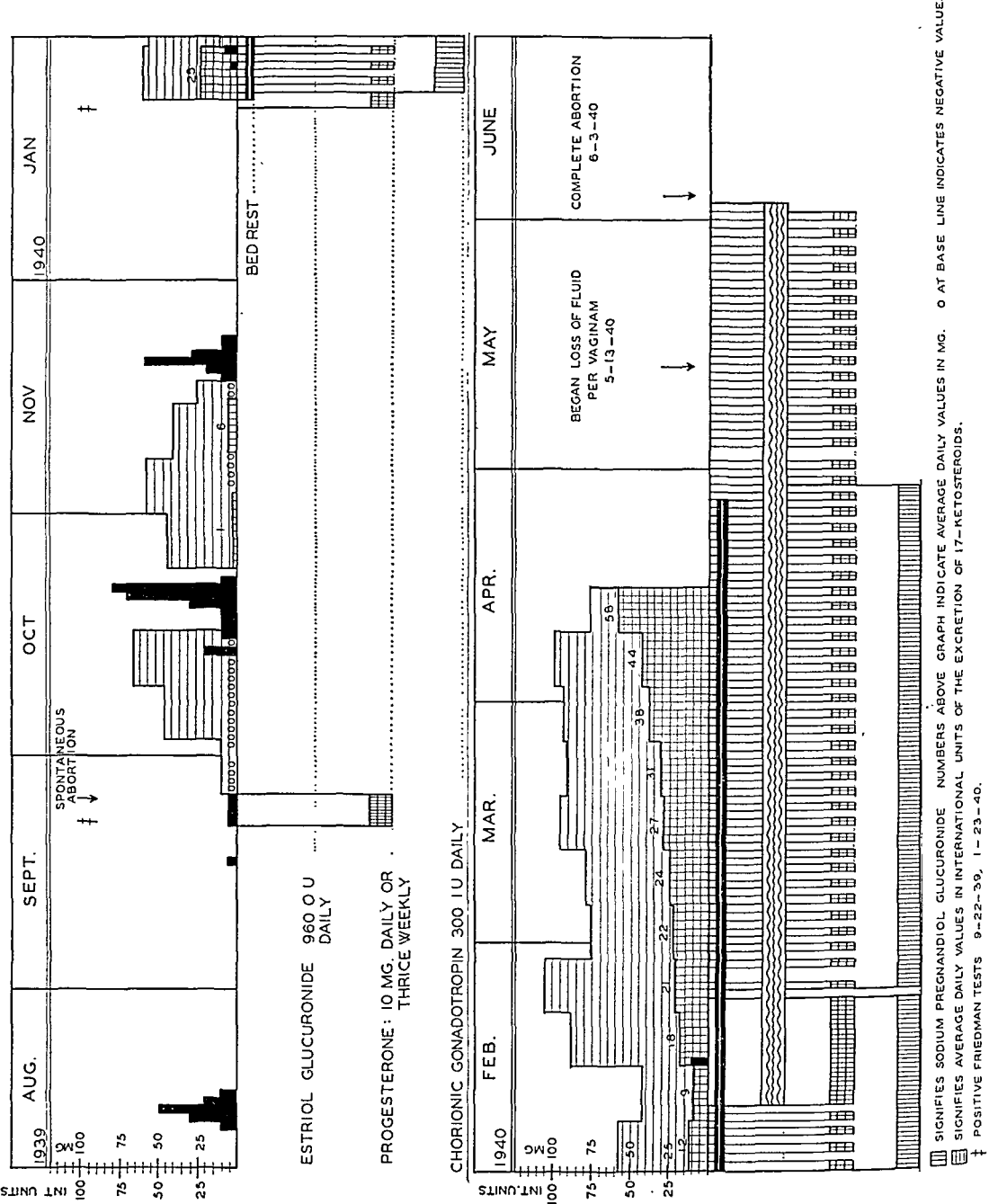


Fig. 4.—Case 4. Graphic clinical record including various therapies and the urinary excretionary values of pregnanediol complex.

On August 23 the patient reported that she had felt no fetal movements for two days. In view of this apparent fetal death and in view of low urinary titers of pregnanediol complex, therapy was discontinued. On August 26 the patient went into premature labor and delivered a macerated fetus of some seven months' gesta-

showed a gradual and continual rise. Treatment was started as soon as her first period was missed and certainly must be judged to have been adequate. It was our feeling that since the patient carried this pregnancy so much longer than her 3 previous six weeks' abortions and since her pregnanediol titers were quite normal, she might have gone to term had not the premature rupture of membranes occurred. What success therapy attained in this case may well have been due to the thyroid substance rather than to the other agents used.

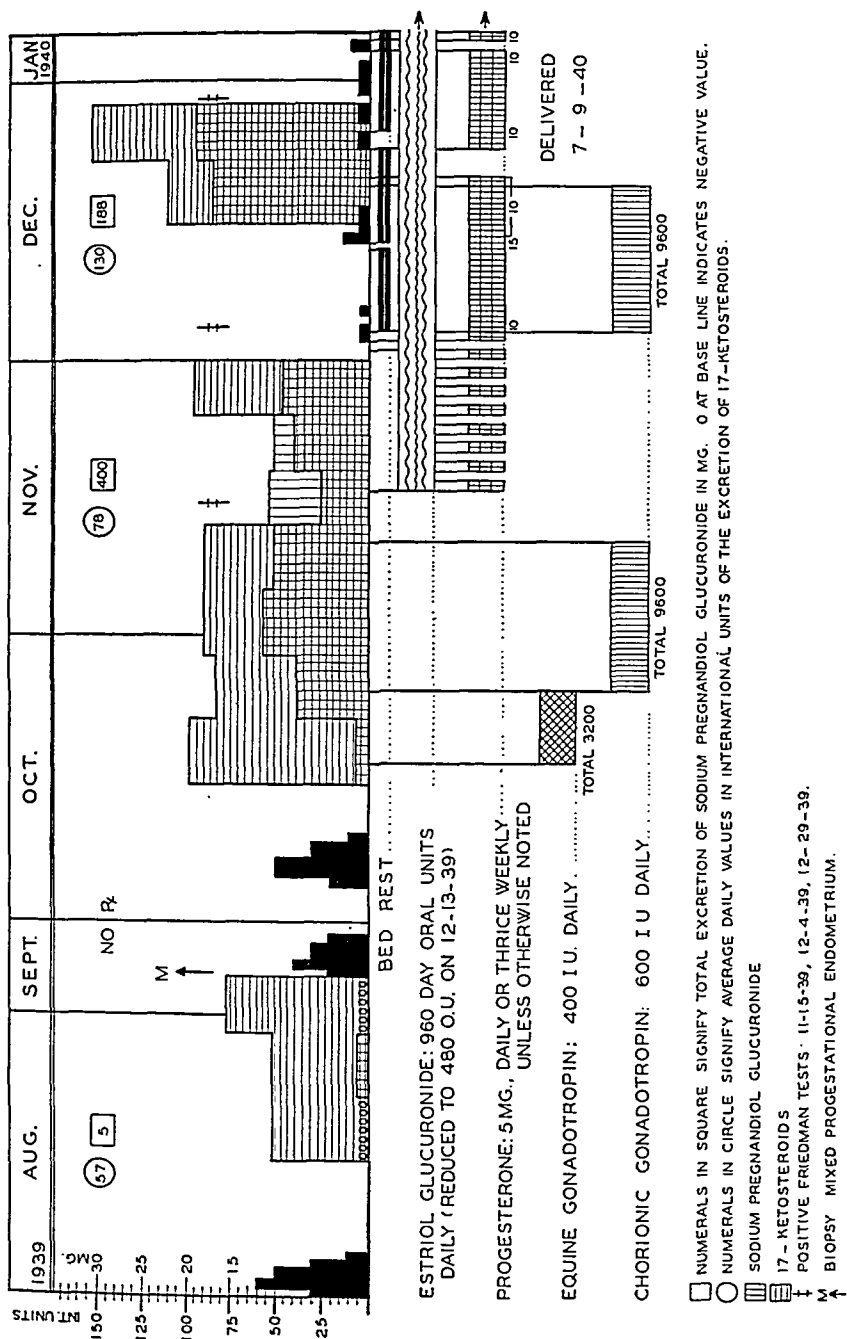


Fig. 3.—Case 3. Graphic clinical record including various therapies and the urinary excretory values of pregnanediol complex.

CASE 5.—Miscarriage at seven months in a patient who had had 3 previous miscarriages or abortions. Treatment with progesterone and chorionic gonadotropins. Mrs. E. W., aged 26 years, para 3-3-0, was referred to the Endocrine Division Jan. 13, 1940, because of a history of three previous abortions or miscarriages. Gyneco-

tion. The placenta was described by the pathologist as being full size with no gross pathologic changes. Microscopic examination likewise revealed no pathologic changes.

Abortion or miscarriage was anticipated from the early stages of pregnancy in this case because of the consistently low pregnanediol titers and because of the fact that even during her third and fourth month of pregnancy they had shown no substantial elevations; as a matter of fact these had started declining during the latter part of the third month. A striking finding was the extremely low values for pregnanediol during the menstrual cycle during which pregnancy occurred. For ten consecutive days during the progestational phase of this cycle, no pregnanediol was excreted, despite the fact that the patient was receiving both progesterone and chorionic gonadotropins.

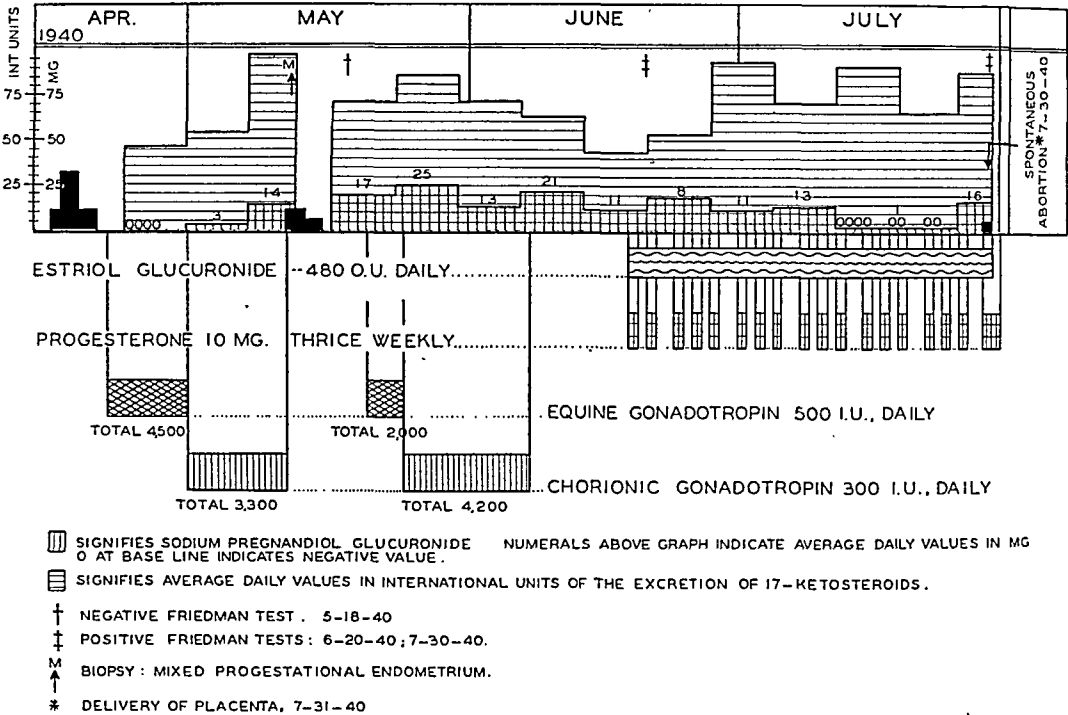


Fig. 6.—Case 6. Graphic clinical record including various therapies and the urinary excretory values of pregnanediol complex.

CASE 6.—Abortion at three and one-half months by a patient who had had 3 previous abortions. Treatment with estriol glucuronide and progesterone. Mrs. L. R., aged 33 years, para 3-3-0, was first seen in the Endocrine Division Sept. 2, 1937. During the patient's previous five years of marriage 3 abortions had occurred at approximately the third month of gestation. Endocrine and gynecologic surveys were essentially negative except for clinical hypothyroidism. The patient's basal metabolic reading when seen first was -21 per cent. During a two-and-one-half-year period of observation and study no pregnancy occurred, despite the fact that metabolic irregularities were adjusted by thyroid substance to full clinical tolerance. These studies embraced quantitation of pregnanediol complex during 4 menstrual cycles with negative results and examinations of a number of endometrial specimens taken at onsets of episodes of bleeding. All of the latter showed estrogenic or minimal progestational responses.

On April 22, 1940, a series of cyclic gonadotropic therapy was instituted which led to a pregnancy. Fig. 6 presents graphically the clinical record from this time on, including therapy, urinary titrations for 17-ketosteroids, and sodium pregnanediol glucuronide. This record covers the cycle preceding pregnancy, the pregnancy, and

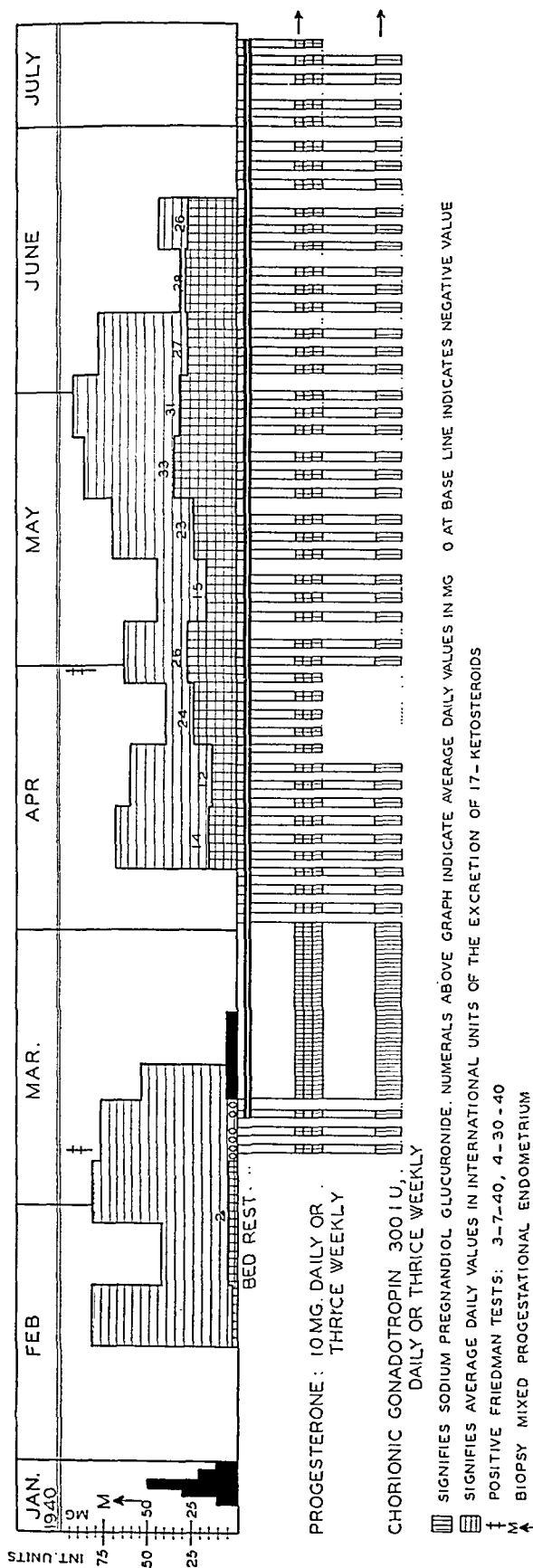


Fig. 5.—Case 5. Graphic clinical record including various therapies and the urinary excretionary values of pregnanediol complex. On August 26, a macerated seven months' fetus was delivered.

It does not seem unlikely that the sterol and chorionic gonadotropic therapy given these patients may have interfered with the usual therapeutic efficacy of thyroid therapy.

The failure of even the large amounts of progesterone employed to increase the pregnanediol output of these patients agrees well with other reported studies of our group in nonpregnant women. At times during these studies, it was observed that the total output of pregnanediol was considerably less than that to be anticipated from the efficient metabolism of the injected progesterone alone. We are inclined, therefore, to believe that intensive progesterone therapy may actually lower the pregnanediol output of patients, i.e., decrease their intrinsic progestin metabolism.

Our observations warrant the belief that studies of urinary titers of the pregnanediol complex are of no clinical value in the diagnosis or treatment of impending or habitual abortion. They likewise indicate that, when low pregnanediol titers are diagnosed, the administration of amounts of progesterone theoretically capable of complementing the calculated pregnanediol deficit fails to effect any significant elevation in these titers.

SUMMARY

Some concepts of the hormonology of abortion have been reviewed and studies of progestin metabolism in patients with histories of repeated abortions have been reported.

The following observations seem warranted from our studies:

1. As a rule, pregnanediol titers tend to fall prior to abortion. This fall may be abrupt or gradual.
2. During the course of pregnancy prior to the onset of abortion titers may be normal or low.
3. Patients may threaten to abort when pregnanediol titers are normal.
4. Intensive therapy with progesterone, alone or combined with estrogens and chorionic gonadotropins, fails to elevate low pregnanediol titers and to prevent abortion.
5. There is a likelihood that large doses of progesterone may precipitate abortion by depressing the metabolism of intrinsic progestin.
6. Progesterone therapy may interfere with the therapeutic efficacy of thyroid substance in preventing abortion in hypothyroidism.
7. Any beneficial effect which therapy with progesterone possesses in the treatment of habitual abortion cannot be explained upon the basis of its complementing deficits in progestin-pregnanediol metabolism.

The progesterone used in these studies was supplied generously by the following concerns: Ciba Pharmaceutical Products, Inc., Summit, N. J. (lutocycin); Eli Lilly & Company, Indianapolis, Ind. (progestin); Schering Corporation, Bloomfield, N. J. (poluton). The chorionic gonadotropins (APL) and the estriol glucuronide (emmenin) were supplied by Ayerst, McKenna & Harrison, Montreal, Canada.

Part of the expenses involved in these studies was defrayed by grants from the Research Council of Duke University and from Schering Corporation, Bloomfield, N. J.

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the patient's spontaneous abortion July 30, 1940. Gross and microscopic examinations of the placenta showed no abnormalities.

Abortion was anticipated in this case during the last six weeks of pregnancy because of the declining pregnanediol titers. There was a period of time just prior to abortion when the patient, despite treatment, excreted no pregnanediol for eight consecutive days; however, during the four days immediately preceding abortion, the patient excreted 16 mg. of pregnanediol and on the day of abortion gave a positive pregnancy test.

A complicating factor was introduced inadvertently in this case due to the fact that an endometrial biopsy was taken apparently at the onset of an episode of bleeding, which subsequently proved to have been most likely of implantational nature. No chorionic tissue was encountered in the endometrium secured at this time. The scantiness of this episode of flowing, the failure of the pregnanediol complex to disappear from the urine after this bleeding ceased, and the increased quantities of it excreted at this time seemed indicative of pregnancy, despite the negative pregnancy test. In 4 other similar instances, accidental biopsies at the time of implantational bleeding or during the first few weeks of pregnancy have been done; in only one of these did abortion occur, and here apparently the entire product of conception was removed during the biopsy. The other 3 patients who had biopsies at this time continued normally to term and delivered healthy babies. The facts that a positive pregnancy test was received the day of abortion, that no pathologic findings were encountered in the placenta, that no symptoms of impending abortion existed until a few hours before the abortion actually occurred, and that low urinary excretory values of pregnanediol had characterized the last six weeks of pregnancy seem to relate the abortion to endocrine rather than to traumatic factors.

This case suggests two significant observations in regard to the hormonology of pregnancy. Significant increases of pregnanediol complex may be recognized in the urine during early pregnancy even prior to the excretion of sufficient concentrations of gonadotropins to yield a positive pregnancy test. Failure of the placental function of progesterin-pregnanediol metabolism may occur prior to, and independently of, any significant alterations in gonadotropic output.

DISCUSSION

Studies of urinary titers of the pregnanediol complex yield equivocal data regarding the hormonology of women giving histories of repeated abortions. In some cases low titers may be encountered throughout the greater part of the pregnancy. In others, a critical fall in these titers does not occur until shortly before actual abortion. Abortion may threaten and, perhaps, may occur when the pregnanediol titers are normal (Case 3).

Our observations have indicated that when abnormally low pregnanediol titers are encountered, intensive therapy, even when initiated as soon as pregnancy is diagnosed, is unable to restore normal excretory values or to prevent abortion. This is true of various combinations of therapy: Progesterone intramuscularly in oil in daily or thrice weekly doses varying from 5 to 10 mg.; similar amounts of progesterone combined with estrogens or with estrogens and chorionic gonadotropins (during first three to four months of pregnancy). The failure of this latter combination of therapy to prevent abortion in the patients in Cases 4, 5, and 6 warrants analysis. These 3 patients had varying grades of hypothyroidism and received in addition to the therapy mentioned, thyroid substance to full clinical tolerance. Had thyroid substance alone been given, better results would have been expected than those obtained.

imals were considered to be in good physical condition and were found to be free of spontaneous disease at autopsy.

In the three weeks' control period which preceded the production of renal injury in each of these animals, blood pressure determinations were made by an indirect method⁸ twice weekly, urine specimens were collected in metabolism cages and examined for albumin and sediment weekly, and two blood samples were taken for determination of nonprotein nitrogen. Following the procedure carried out to produce renal injury, the blood pressure was determined daily, the urine was examined and the nonprotein nitrogen determination made every other day, until the animal had died or was sacrificed.

All animals not dying within the period of one week were sacrificed by means of 10 per cent formalin intravenously. Routine autopsies were immediately performed; blocks were fixed in Helly's modification of Zenker's solution, embedded in paraffin and stained with hematoxylin and eosin.

In choosing the nephrotic substances an effort was made to use those substances which act more or less specifically on a separate part of the renal apparatus; uranium nitrate,¹¹ sodium oxalate,⁴ and staphylococcus toxin¹² were used. In another group of animals, bilateral ureteral ligation was performed to determine whether this type of renal injury would produce alteration in reaction in the pregnant animal. Many investigators have presented evidence to suggest that ureteral obstruction, pyelitis, and pyelonephritis during pregnancy are predisposing factors to the toxemias of pregnancy.¹³ Hypertension has been shown to be present in clinical¹⁴ and experimental¹⁵ ureteral obstruction, and its origin is possibly the same as that seen with renal artery constriction.

In each of the toxins used, an effort was made to employ from one-fourth to one average lethal dose to similar groups of pregnant and nonpregnant animals.

Uranium nitrate was given intravenously in doses of 0.25 mg. and 0.5 mg. per kilogram body weight. Sodium oxalate was given in 3 doses in twelve hours of a 2 per cent solution of normal saline in total doses of 30, 60, and 80 mg. per kilogram body weight, to both pregnant and nonpregnant animals.

Staphylococcus toxin* was given intravenously in 0.025, 0.05 and 0.1 c.c. to both pregnant and nonpregnant animals in two doses in four hours.

Ureteral ligation was performed in the animals of the last group. Under aseptic technique the ureters were doubly ligated and severed, at the junction of the ureter with the renal pedicle.

RESULTS

Uranium Nitrate.—Table I shows the effect of this toxin on four pregnant and four nonpregnant adult rabbits.

The smallest dosages employed (one-fourth of the average lethal dose)¹¹ caused no change in general condition, nonprotein nitrogen values of the blood, nor significant albuminuria in the pregnant animals. In the nonpregnant animals, however, more apparent injury was sustained; moderate to marked albuminuria, moderate elevations in blood nonprotein nitrogen, and a slight depreciation in general condition were noted. In neither group was there noted to be a significant change in blood pressure, evidence of pathologic liver injury or more than minimal renal injury.

No abortions of fetuses were noted in this group.

The use of the larger dosages (one-half of the average lethal dose) caused a noticeable depression of general condition in both groups of animals and marked albuminuria was uniformly present. The blood nonprotein nitrogen became elevated in all instances and severe renal injury was noted pathologically.

No significant alteration in blood pressure occurred, and the liver showed no gross or microscopic lesions. The difference between the severity of reaction of the two groups is also less marked than in the previous group, and it is noticeable that all pregnant animals delivered or resorbed by the fourth day.

*The staphylococcus toxin used in this study was provided by Dr. A. L. Joyner and the Lederle Laboratories.

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THE EFFECT OF PREGNANCY ON EXPERIMENTALLY PRODUCED RENAL INJURY

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INTRODUCTION

THE tendency to associate the hypertensive syndromes in pregnancy with injury to the kidney has resulted from observations that water retention becomes obvious early in the disease,¹ that albuminuria is almost always present, and that nitrogen retention, although inconstant and later in appearance, is of frequent enough occurrence to point toward the renal system.² This view has been further strengthened by the demonstration that certain types of renal injury may cause transient hypertension,³⁻⁵ that permanent elevations of blood pressure accompany reduction of the renal blood flow,⁶ and that reduction of renal blood flow in the experimental animal causes a syndrome which closely resembles "eclampsia" in the human being.^{7, 8}

The production of renal injury in the experimental animal has been thoroughly investigated and many different types of nephrotoxic substances have been used.⁹ It is of interest, however, that only a few of these agents produce a noticeable degree of hypertension and none produces albuminuria of marked degree without nitrogen retention.¹⁰

We have been impressed by the severity of the reaction of the pregnant animal to renal ischemia as compared to that of the nonpregnant one. A review of the literature fails to reveal any evidence to show that other types of renal injury in pregnancy produce a significant difference in reaction. These experiments were designed in an effort to demonstrate the reaction of pregnant animals to various nephrotoxic substances as compared with the nonpregnant animal.

MATERIALS AND METHODS

Thirty-nine female rabbits of from 2.5 to 3.5 kilograms body weight were used as the experimental animals. Twenty-three of these animals were known to be of from eighteen to twenty-two days in the period of gestation and the remaining 16 had been segregated for approximately three weeks to rule out pregnancy and pseudo-pregnancy. Food consisted of a stock rabbit food and water ad libitum. All ani-

TABLE II. THE EFFECT OF SODIUM OXALATE ON THE GENERAL CONDITION, BLOOD PRESSURE, AND RENAL STATUS OF THE PREGNANT AS COMPARED WITH THE NONPREGNANT RABBIT

RABBIT NO.	DOSAGE	ALBUMINURIA*		BLOOD PRESSURE†		GENERAL CONDITION	HIGHEST N.P.N.	AUTOPSY		OUTCOME OF PREGNANCY
		AMOUNT	DAYS	BEFORE	AFTER			KIDNEYS	LIVER	
75	30 mg.	0	0	100	95	Good	48.2	Minimal injury	Neg.	Resorbed on third day
76	30 mg.	0	0	90	80	Good	52.5	Minimal injury	Neg.	Delivered on fourth day
61	60 mg.	tr.	6	75	110	Good	101.5	-----	---	Delivered on fourth day
65	60 mg.	3+	5	70	90	Good	80.2	Moderate injury	Neg.	Resorbed on fifth day
64	80 mg.	3+	4	90	80	Fair	243.0	Severe injury	Neg.	Resorbed on fifth day
58	80 mg.	3+	4	95	120	Good	144.0	Severe injury	Neg.	Delivered on fourth day
68	30 mg.	0	0	100	105	Good	46.4	Neg.	Neg.	Nonpregnant
62	60 mg.	tr.	6	90	100	Good	46.0	-----	---	Nonpregnant
63	80 mg.	tr.	4	75	110	Good	42.0	-----	---	Nonpregnant
54	80 mg.	3+	5	100	120	Fair	200.0	Moderate injury	Neg.	Nonpregnant

* † See footnotes, Table I.

TABLE I. THE EFFECT OF URANIUM NITRATE ON THE GENERAL CONDITION, BLOOD PRESSURE, AND RENAL STATUS OF THE PREGNANT AS COMPARED WITH THE NONPREGNANT RABBIT

RABBIT NO.	DOSAGE	ALBUMINURIA*		BLOOD PRESSURE†		GENERAL CONDITION	HIGHEST N.P.N.	AUTOPSY		OUTCOME OF PREGNANCY
		AMOUNT	DAYS	BEFORE	AFTER			KIDNEYS	LIVER	
80	0.25 mg.	0	0	90	90	Good	43.1	Neg.	Neg.	Pregnant at time of sacrifice
77	0.25 mg.	1+	4	100	80	Good	51.1	Neg.	Neg.	Pregnant at time of sacrifice
45	0.5 mg.	4+	6	95	112	Fair	62.2	Minimal injury	Neg.	Resorbed on fourth day
56	0.5 mg.	3+	4	85	118	Fair	175.0	Moderate injury	Neg.	Delivered prematurely on fourth day
49	0.25 mg.	3+	5	95	95	Fair	94.6	Moderate injury	Neg.	Not pregnant
53	0.25 mg.	3+	20	65	65	Fair	91.0	-----	----	Not pregnant
52	0.5 mg.	4+	6	100	115	Died	252.0	Severe injury	Neg.	Not pregnant
55	0.5 mg.	3+	6	85	110	Good	128.0	Severe injury	Neg.	Not pregnant

*The symbols under "albuminuria" represent:

Amount: tr., No precipitate after heating, slight clouding after acid.

1+, Granular precipitate after heating.

2+, Heavy granular precipitate after heating.

3+, Heavy flocculate precipitate after heating and acid.

4+, Boils solid on heating.

Days: The number of days the albuminuria was present.

†Under "blood pressure" the figures represent the average of blood pressures taken before and after production of renal injury.

One animal in the nonpregnant group died of uremia; no deaths were encountered in the pregnant group.

Sodium Oxalate.—Table II shows the effect of intravenous injections of varying dosages of sodium oxalate on 6 pregnant and 4 nonpregnant adult rabbits.

All animals, both pregnant and nonpregnant, following injection with the smallest dosages of sodium oxalate showed no significant change in general condition, urinary findings, or blood pressure, and no nitrogen retention was noted. Pathologic study revealed no renal or hepatic damage. Both pregnant animals resorbed the fetuses or delivered by four days, however.

Moderate dosages of sodium oxalate produced mild elevation of blood pressure and slight albuminuria in both groups of animals. The general condition remained good and no abnormal hepatic pathology was noticeable, although renal injury was present to a minimal degree. An elevation of blood nonprotein nitrogen was noted only in the pregnant group and resorption or delivery of fetuses was accomplished in both instances by the fourth day.

Large doses of sodium oxalate produced a mild elevation of the blood pressure, moderate albuminuria, and marked elevation of the blood nonprotein nitrogen in both pregnant animals and in one of the two nonpregnant ones. The remaining nonpregnant animal showed evidence of renal injury, but not of such severe nature. All pregnant animals had resorption or delivery of fetuses by the fifth day. Pathologic sections showed marked renal injury but no hepatic damage.

Staphylococcus Toxin.—Table III shows the effect of varying dosages of this toxin on 7 pregnant and 7 nonpregnant adult female rabbits.

The animals receiving very small doses of this substance showed no evidence of clinical or pathologic injury.

In general all animals, both pregnant and nonpregnant, receiving moderate dosages, remained normal. In one animal in each group, however, moderate to severe albuminuria, nitrogen retention, and severe damage to the renal cortex pathologically were noted. Two animals in the pregnant group were noted to have rare areas of midzonal necrosis of the liver lobule; one of these had severe renal injury. Significant alterations in blood pressure were not noted in any of these animals.

All animals receiving the larger dosages of toxin died immediately after injection and no pathologic lesions were noted.

Large doses produced severe albuminuria, a moderate elevation in blood pressure and nitrogen retention in both the pregnant and nonpregnant groups of animals. Pathologically the renal damage was noted to be severe; in one animal rare but definite midzonal areas of necrosis in the liver were noted. The resorption of fetuses occurred in all pregnant animals.

It seemed quite noticeable in all animals except one that the pregnant animal received more injury from this drug than that noted in the nonpregnant one, as evidenced by the degree of albuminuria, level of the nonprotein nitrogen in the blood, and pathologic evidence of renal injury. No significant difference in the blood pressure levels could be determined.

Ureteral Ligation.—Ureteral ligation produced a steadily rising nonprotein nitrogen level in the blood and a depression of the general condition in all animals. All nonpregnant animals developed a mild rise of blood pressure but all but one of the pregnant animals had a decided fall in pressure. Delivery was noted in two of the pregnant animals before death.

Pathologic sections showed extreme damage to the kidneys but no evidence of injury to the liver.

The effect of ureteral ligation on 3 pregnant and 3 nonpregnant adult rabbits is given in Table IV.

DISCUSSION

It seems that the response of the pregnant animal toward different types of renal injury differs slightly from that of the nonpregnant animal and also with the type of injury produced.

TABLE III. THE EFFECT OF STAPHYLOCOCCUS TOXIN ON THE GENERAL CONDITION, BLOOD PRESSURE, AND RENAL STATUS OF THE PREGNANT AS COMPARED WITH THE NONPREGNANT RABBIT

RABBIT NO.	DOSAGE C.C.	ALBUMINURIA*		BLOOD PRESSURE†		GENERAL CONDITION	HIGHEST N.P.N.	AUTOPSY		OUTCOME OF PREGNANCY
		AMOUNT	DAYS	BEFORE	AFTER			KIDNEYS	LIVER	
35	0.025	0	0	90	90	Good	42.0	Neg.	Neg.	Pregnant at time of sacrifice
57	0.050	4+	1	100	90	Died	100.0	Severe injury	Necrosis	Delivered at five days
85	0.050	0	0	85	85	Fair	69.0	Minimal injury	Neg.	Pregnant at time of sacrifice
59	0.050	0	0	115	125	Good	54.0	Neg.	Neg.	Pregnant at time of sacrifice
86	0.050	0	0	105	110	Good	44.8	Minimal injury	Neg.	Pregnant at time of sacrifice
36	0.10	0	0	---	---	Died	---	Neg.	Neg.	Died one hour after injection
37	0.10	0	0	---	---	Died	---	Neg.	Neg.	Died one hour after injection
38	0.025	0	0	90	90	Good	40.0	Neg.	Neg.	Nonpregnant
88	0.050	0	0	95	100	Good	36.7	Neg.	Neg.	Nonpregnant
60	0.050	2+	4	90	90	Poor	160.0	Neg.	Neg.	Nonpregnant
87	0.050	0	0	112	110	Good	53.3	Neg.	Neg.	Nonpregnant
75	0.050	0	0	100	95	Good	48.0	Minimal injury	Neg.	Nonpregnant
39	0.10	0	0	---	---	Died	---	Neg.	Neg.	Died one hour after injection
40	0.10	0	0	---	---	Died	---	Neg.	Neg.	Died one hour after injection

* † See footnotes, Table I.

TABLE IV. THE EFFECT OF BILATERAL URETERAL LIGATION ON THE GENERAL CONDITION, BLOOD PRESSURE, AND RENAL STATUS OF THE PREGNANT AS COMPARED WITH THE NONPREGNANT RABBIT

RABBIT NO.	PROCEDURE	ALBUMINURIA*		BLOOD PRESSURE†		GENERAL CONDITION	HIGHEST N.P.N.	AUTOPSY		OUTCOME OF PREGNANCY
		AMOUNT	DAYS	BEFORE	AFTER			KIDNEYS	LIVER	
73	Ureters ligated	---	---	90	too low	Died	166	---	---	Delivered at four days
74	Ureters ligated	---	---	90	too low	Died	90	Severe injury	Neg.	Pregnant at time of sacrifice
66	Ureters ligated	---	---	100	115	Died	168	Severe injury	Neg.	Delivered at four days
67	Ureters ligated	---	---	90	100	Died	150	Severe injury	Neg.	Nonpregnant
70	Ureters ligated	---	---	100	135	Died	200	---	---	Nonpregnant
69	Ureters ligated	---	---	100	110	Died	224	---	---	Nonpregnant

* † See footnotes, Table I.

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THE METABOLISM OF PROGESTERONE IN THE HYSTERECTOMIZED WOMAN

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THE role of the uterine endometrium as a metabolic or endocrine organ has long been of interest to both the physiologist and clinician. Numerous observations have been made on experimental animals which tend to support the theory of such a uterine function. Most notable among these is the classic work of Loeb in which he demonstrated that a persistent corpus luteum followed hysterectomy in the guinea pig.

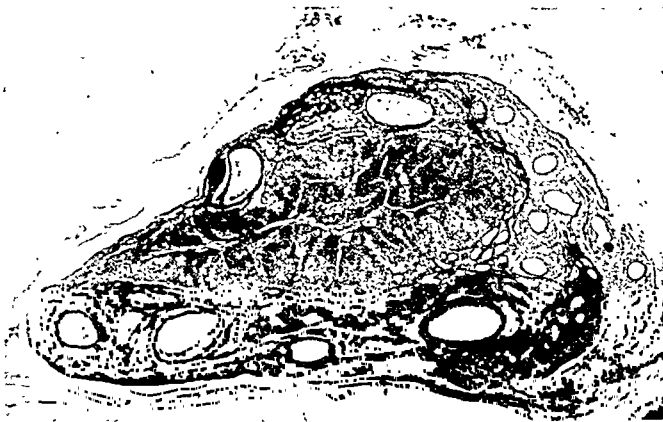


Fig. 1.—Low power photomicrograph of the ovary of a monkey *Macacus* (*Pithecus*) *rhesus*, removed 15 months after a panhysterectomy. Monkey 21, through the courtesy of Dr. Carl G. Hartman of the Carnegie Institution.

This work has recently been repeated on the rabbit by Asdell and Hammond. No one, however, has demonstrated such a mechanism in the primates, and Hartman has observed regular ovulations following hysterectomy in the *Macacus rhesus*. Through the courtesy of Dr. Carl Hartman of the Carnegie Institution, the ovarian sections of one of his hysterectomized monkeys has been made available to us for publication (Fig. 1). The case history of this animal, No. 21, has been presented in the Contributions to Embryology for 1928, and is interesting in that she continued to have vaginal estrous cycles and changes in the sex swelling as long as fifteen months after a panhysterectomy. A histologic examination of the ovaries at autopsy showed numerous primordial follicles, Graafian follicles in all stages of development, and

Uranium nitrate seems to exert a somewhat less harmful effect during pregnancy, while sodium oxalate seems more injurious. The difference in individual susceptibility of animals to staphylococcus toxin and the fact that all animals with ureteral ligation die in uremia with marked renal destruction makes the effect of these two types of renal injury harder to evaluate; however, the pregnant animal does not seem to differ significantly in response from the nonpregnant animal.

Any striking variation in reaction which might be expected in the pregnant animal is undoubtedly modified by the fact that abortion or resorption of fetuses generally occurs soon after the production of kidney injury; in this way the effects of pregnancy are exerted only in the earliest stages of the experiment.

Significant variations in blood pressure are not noted following renal injury by uranium or staphylococcus toxin. Ligation of the ureters seems to produce a modest rise in pressure in the nonpregnant animal, but none in the pregnant one, while sodium oxalate produces a mild elevation of pressure in both the pregnant and nonpregnant animals.

No significant constant necroses in the liver or other organs were produced by any of these substances except the staphylococcus toxin, and these are found in the nonpregnant as well as in the pregnant animal. The small number of animals in this series makes evaluation of such injury in the presence of extreme differences in susceptibility of individual animals extremely hazardous, but this type of injury seems quite promising for further investigation.

None of these methods will reproduce with regularity either the clinical picture, the pathologic changes, or the increased susceptibility in the pregnant state such as that seen following constriction of the renal arteries of the rabbit. It seems that the renal ischemia, both in the pregnant and nonpregnant animal is not the result of nonspecific injury as such but is a definite entity caused by a specific type of alteration of renal physiology.

CONCLUSIONS

Pregnancy does not exert a deleterious effect on all types of renal injury.

The pregnant animal seems to be minimally less susceptible than the nonpregnant one to uranium nitrate, slightly more susceptible to sodium oxalate, and demonstrates no significant difference to staphylococcus toxin or ureteral ligation.

The syndrome produced by renal artery constriction in the pregnant and nonpregnant animal is not due to renal damage as such, but is apparently caused by a relatively specific type of altered renal physiology.

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Smith and Smith who, in 1939, concluded that progesterone, acting through the uterus (presumably the endometrium) brings about the conversion of estrone to estriol. The evidence of this, however, does not seem to be based on any studies in the hysterectomized human being but on work performed on the rabbit by Pincus and Zahl. In this work five hysterectomized rabbits were injected with estradiol and estrone in various experiments and the partition of the estrogenic substances was estimated in the urine. The David color reaction was used as a measure of estriol and the phenol-sulfonic acid and sulfanilic acid tests of the estrone and estradiol excretion. Although this work is interesting it would seem that isolation of the true chemical substances would be a much safer basis for so broad a theory.

With the publication of the Browne and Venning method for the determination in the urine of sodium pregnanediol glucuronide, the excretion product of the corpus luteum, a third and more satisfactory technique for the study of the hormonal metabolism of the uterus, has become available. This approach offers two great advantages over the former methods. First, the method is chemically accurate, and second, it demonstrates the presence of a functioning corpus luteum, which is commonly assumed to be an index of ovulation and is therefore better proof of the normal cyclical function of the ovary.

The problem has been approached from this angle by several observers. Browne and Venning, in the discussion of a paper which appeared in 1937, first suggested that pregnanediol failed to appear in the urine of hysterectomized women who had been injected with progesterone, indicating a failure of conversion of progesterone into pregnanediol in the absence of the uterus. A further note was published in 1938 in which it was stated that two hysterectomized patients, each of whom had been injected with 24 mg. of progesterone, failed to excrete pregnanediol. In 1940, however, they report the recovery from the urine of a hysterectomized patient of 8.6 mg. of pregnanediol after the injection of 90 mg. of progesterone over a three-day period. Hamblen in 1937, on the basis of a study of four cases, concluded that the endometrium was necessary for the conversion of progesterone into pregnanediol. An analysis of his cases shows that only one was hysterectomized and this patient excreted 4 mg. of sodium pregnanediol glucuronide on the fourth day postoperatively. The other three cases studied were patients upon whom a dilatation and curettage had been performed. Of these, one was operated upon on the twenty-third day of the cycle. She excreted 2.6 mg. of the pregnanediol complex the first day postoperatively and none the second day, that is the twenty-fifth day of the cycle. From the figures of Browne and Venning very little, if any, pregnanediol is excreted so late in the luteal phase of the cycle and small amounts in a twenty-four-hour specimen can easily be lost through technical errors. The second patient, who was curetted on the twenty-third day of the cycle, failed to excrete pregnanediol following the procedure. However, as this patient was not excreting pregnanediol before curettement, the case is of little value. The third patient was operated upon on the twenty-fifth day of the cycle and was excreting only 1.4 mg. of the pregnanediol preoperatively, which probably means that this patient was at the end of her luteal phase. It is, therefore, not surprising that on the twenty-sixth and twenty-seventh days of her cycle she excreted no pregnanediol. Criticism of this work seems justifiable, in that too few cases have been used to draw any conclusions from such purely negative evidence. It is also erroneous to assume that a dilatation and curettage removes all or nearly all of the endometrial tissue.

Stover and Pratt, in 1939, reported the case of a patient upon whom a hysterectomy was performed on the one hundred and forty-second day of pregnancy. This

several corpora lutea aberrantia. Dr. Corner has been kind enough to examine the slides and feels that, although the corpora probably date from several months back, it is unlikely that they are over a year old.

A much earlier piece of work is that published by Mandl and Buerger in 1904. These observers examined the ovaries of apes from six months to three years after hysterectomy and found follicles in all stages of development, including well-formed corpora lutea; however, fewer primordial follicles were seen and blood was noted in many of the larger follicles. The authors, therefore, concluded that there may be some questionable atrophy of the ovaries following hysterectomy in the ape. Glaevecke, Vineberg and Grammatikati each performed similar examinations on human ovaries, six months to three years after removal of the uterus, and were unable to demonstrate any histologic changes from the normal. Such experiments are, of course, open to criticism, in that they attempt to judge function on the basis of morphology.

Aside from these early histologic efforts, the problem in the human being has been approached by three different methods. The first of these was a clinical study of the onset of menopausal symptoms following hysterectomy. The results of such studies were inconstant and interpretation was difficult. Although some authors believe that hysterectomy induces a premature menopause, the possibility of damage to the ovary, through interference with its blood supply at operation, is a factor which must always be considered in studies of this type and which cannot be accurately evaluated.

The older literature on this subject is well summarized by Graves in a paper in 1917. All observers up to that time, with the exception of Dickinson, were of the opinion that hysterectomy alone was as frequently followed by menopausal symptoms as was hysterectomy and bilateral salpingo-oophorectomy. Graves' figures agree with this majority opinion, for, in his series, 80 per cent of 233 cases of hysterectomy and bilateral salpingo-oophorectomy and 81 per cent of 26 cases of simple hysterectomy were associated with menopausal symptoms. TeLinde and Darner, in a more evenly divided series of 98 cases, found that 74 per cent of 52 women, who had had the radical operation, developed menopausal symptoms, while they appeared in only 47 per cent of 46 cases after a simple hysterectomy. It was also noted that the severity of symptoms was much greater following hysterectomy and bilateral salpingo-oophorectomy than after the more conservative operation. Cystic ovaries were never seen postoperatively in those cases where it was possible to retain the Fallopian tubes. That the problem is still a subject of debate can be seen from a discussion by A. H. Curtis in the *American Gynecological Society Transactions* of 1939 in which he states "If the cervix is removed the ovaries degenerate in two to three years; naturally, if the cervix is left the ovaries do not degenerate."

The second approach to the problem came with the advent of blood and urine estrogen determinations. Tamis, in 1934, and Marx, Catchpole and McKennon, in 1936, attempted to evaluate ovarian function after hysterectomy by correlating menopausal symptoms with estrogenic excretion. Here again the results were equivocal. Although methods for estrogen determination have greatly improved since the publication of these reports, the chemical accuracy of such studies is still highly questionable. The most recent work along these lines is probably that of

however, as more attention was given to the purity of the pregnanediol recovered than to the completeness of the recovery. The combined pregnanediol precipitates were frequently precipitated 3 times instead of the customary two. The melting points of the combined pregnanediol specimens ranged between 257° and 266° C. uncorrected, and the free between 222° and 234° C. uncorrected.

As the amount of progesterone injected in these cases was more than that used by most other investigators and was also injected over a period of three days, a hysterectomized case was injected with only 60 mg. of progesterone over a period of six hours. It was thought that such a case might be more comparable to those reported in the literature. Twenty-four-hour collections were made during the injection period and over the two succeeding days. Traces of pregnanediol were recovered on all three days, but the amounts were too small to be identified by melting points.

GROUP 2.—The next case studied was a patient who had had a panhysterectomy on the first day of her menstrual cycle. Pregnanediol determinations were performed on the forty-eight-hour specimens of urine on the twelfth and thirteenth and on the fourteenth and fifteenth days of the cycle. No pregnanediol could be demonstrated. On the sixteenth and seventeenth days 6.1 mg. of the pregnanediol complex, having a melting point of 264° to 265° F., was recovered.

GROUP 3.—Three cases, which had had hysterectomies performed six months or more previously, were studied by following the cervical mucous secretion weekly during a period of one month. All three patients exhibited changes in the pH, viscosity, and the spermatozoa penetrability indicative of a normal ovarian cycle. From these studies it was attempted to approximate the luteal phase and a twenty-four-hour collection of urine was obtained during this period. Three and three-tenths milligrams of pregnanediol was recovered in one out of three of these specimens. It is felt that, because of the very rough approximation of the time of the luteal phase in these patients, it is not surprising that two of the twenty-four-hour specimens were negative.

DISCUSSION

The data which have been presented seem to demonstrate that the presence of the uterine endometrium is not necessary for the conversion of progesterone into pregnanediol. It is probable that the normal ovarian cycle, with the formation of the corpus luteum, is uninterrupted following hysterectomy. This fact is supported by the occurrence of normal amounts of pregnanediol in the urine of two women, one of whom was hysterectomized on the first day of the current menstrual cycle and the other more than six months before.

It has never been possible, in this laboratory, to recover more than 15 per cent of injected progesterone as pregnanediol. Recovery is more satisfactory if the patient is injected over a period of days. It is felt that some of the negative results in the literature might be explained on the basis of inadequate amounts of hormone injected.

SUMMARY

Progesterone has been injected into hysterectomized women and recovered, in part, in the urine as pregnanediol. The percentage recovered was the same as that observed for a normal woman in the follicular phase of the cycle who was injected with an equal amount of the hormone. Pregnanediol, in amounts comparable to those found in normal cyclic women, was recovered from the urine of hysterectomized women at a time when they were estimated to be in the luteal phase of the cycle.

patient continued to excrete pregnanediol during the first five days postoperatively. The authors raise the question of the possibility of stored pregnanediol.

The present study was undertaken in an attempt to evaluate such conflicting results in the literature. An effort was first made to determine the percentage of progesterone which was recoverable as pregnanediol in a normal woman in the follicular phase of the cycle. Pregnanediol determinations were then made on the urine of hysterectomized women who had been injected with progesterone and also on several patients who were estimated to be in the luteal phase of the cycle by testing the cervical mucus. In this way it has been possible to gain some idea of both exogenous and endogenous progesterone metabolism. The pregnanediol determinations were performed by a modification of the Browne and Venning technique previously described.

CASES

GROUP 1.—A normal woman in the follicular phase of her cycle was given an injection of 120 mg. of crystalline synthetic progesterone* in 10 mg. doses, four times a day, over a period of three days. The urine was collected over the entire injection period and the sodium pregnanediol glucuronidate content was determined. With this figure as an index of possible recovery, 3 hysterectomized patients were injected in a similar manner and pregnanediol determinations were performed on the urine. Pregnanediol was recovered in amounts comparable to those found in the patient with endometrium intact (Table I). It can be seen from the table that not more than 15 per cent of the injected progesterone has been recovered as pregnanediol. These figures should not be used as an absolute index of recovery,

TABLE I

PATIENT	OPERATION	PROGESTERONE INJECTED	PREGNANEDIOL* RECOVERED	TOTAL % RECOVERED
D. A.	None	1st day 40 mg. 2nd day 40 mg. 3rd day 40 mg.	<div style="display: flex; align-items: center;"> <div style="margin-right: 5px;">}</div> <div> 9.5 mg. 4.3 mg. <hr/> 13.8 mg. </div> </div>	11.5
J. B.	Panhysterectomy	1st day 40 mg. 2nd day 40 mg. 3rd day 40 mg. 4th day none 5th day none	<div style="display: flex; align-items: center;"> <div style="margin-right: 5px;">}</div> <div> 2.6 mg. 7.2 mg. 4.7 mg. <hr/> 14.5 mg. 4.2 mg. <hr/> 18.7 mg. </div> </div>	12.0 15.6
M. S.	Hysterectomy Bilateral sapingo- oophorectomy	1st day 60 mg. 2nd day 60 mg. 3rd day 60 mg. 4th day none 5th day none	<div style="display: flex; align-items: center;"> <div style="margin-right: 5px;">}</div> <div> 5.3 mg. 3.5 mg. 9.6 mg. <hr/> 18.4 mg. 3.0 mg. 1.9 mg. <hr/> 23.3 mg. </div> </div>	10.2 12.9
M. M.	Hysterectomy	†1st day 60 mg. 2nd day 60 mg. 3rd day 60 mg.	<div style="display: flex; align-items: center;"> <div style="margin-right: 5px;">}</div> <div> 4.9 mg. 9.6 mg. 5.1 mg. <hr/> 19.6 mg. </div> </div>	10.9

*Values calculated as free pregnanediol according to Venning: J. Biol. Chem. 126: 595, 1938.

†Twenty-sixth day of calculated cycle.

*Synthetic lutocycin through the courtesy of the Ciba Corporation.

progesterone therapy appeared to be indicated. These cases are divided into several groups; namely, habitual or threatened abortion, dysmenorrhea, and functional bleeding. In the latter two groups, we were able to obtain endometrial biopsies before and after treatment.

Under $\frac{1}{2}$ per cent novocaine anesthesia, an incision less than 1 cm. in length is made in the skin in the region of the left groin. A channel, 2 cm. in length, is made with a small curved hemostatic forceps. The forceps are withdrawn, and the pellet inserted into the bed thus formed. The edges of the incision are strapped together with sterile adhesive. No sutures are used. This procedure takes but a few seconds longer than an intramuscular injection. The incision heals by primary union within twenty-four hours. No immediate adverse symptoms or side reactions have been observed. However, in 35.7 per cent of the cases, the pellet has been expelled spontaneously two or three weeks after implantation. In these cases, reimplantation has been performed successfully.

GROUP I. HABITUAL AND THREATENED ABORTION

Four cases were observed. One, delivered at full term, is briefly described as follows:

M. S., aged 28 years: Habitual abortion following primary sterility. Previous treatment for sterility: thyroid, and substitution estrone and progesterone therapy by intramuscular injection. No results. X-ray stimulation to pituitary and ovaries. Conception one month later. Spontaneous miscarriage at five months. Patient conceived four months later and miscarried again at six weeks. Two months later conception took place for the third time. At four and one-half months patient experienced cramps similar to those at time of first miscarriage. Implantation with 62.8 mg. of progesterone was done May 16, 1940. This pellet was expelled spontaneously on June 3, 1940. Reimplantation of 45 mg. was done the same day. Pains completely disappeared a few days after first implantation and the pregnancy continued uneventfully to term.

The other cases are still under observation. It should be noted that no miscarriage occurred in any of the 4 patients treated.

M. S., aged 34 years: Habitual abortion. History of spontaneous miscarriage at two and one-half months in 1937, and at three and one-half months in 1939. Last menstrual period March 5, 1940. Implantation of 52 mg. of progesterone was done June 3, when the patient was eight weeks gravid. The course of this pregnancy has been uneventful to date (eight months). (Courtesy of Dr. Lyman Burnham.)

D. F., aged 28 years: Threatened abortion. History of spontaneous miscarriage at two months in 1939. Last menstrual period July 30, 1940. Patient reported spotting on several occasions during this pregnancy. Implantation of 49 mg. of progesterone on Sept. 9, 1940, when patient was six weeks gravid. There has been no spotting since September 11; pregnancy at present is of three months' duration. (Courtesy of Dr. Lyman Burnham.)

J. T., aged 28 years: Threatened abortion. History of spontaneous miscarriage at three months in 1936. Last menstrual period May 8, 1940. Cramps and vaginal bleeding Aug. 12, 1940. Implantation of 49 mg. of progesterone on Sept. 20, 1940. Pains subsided after implantation. Examination Nov. 14, 1940, disclosed normal pregnancy of six months.

GROUP II. DYSMENORRHEA

T. S., aged 26 years: Primary dysmenorrhea. Examination: uterus normal in size and position. No adnexal masses. Basal metabolic rate -14 per cent. Previous therapy: Pelvic sympathectomy three years ago. Recurrence of symptoms past two years. Biopsy (Fig. 1) taken on March 26, 1940, the eighteenth day of the cycle, revealed moderate proliferative activity, no evidence of secretory phase.

It is estimated that the hysterectomized woman is able to metabolize both exogenous and endogenous progesterone.

The authors wish to express their appreciation to Dr. Landrum B. Shettles for his advice and assistance in the cervical mucus studies and to the Ciba Corporation for a very generous supply of lutocycin.

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A CLINICAL STUDY OF PROGESTERONE THERAPY BY PELLET IMPLANTATION

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PROGESTERONE is now used in clinical gynecology for the treatment of habitual abortion, functional bleeding, dysmenorrhea, and premenstrual tension. Intramuscular injections in doses of 1 to 5 mg. have been the usual method of therapy. Recently, an oral progesterone-like substance, pregnenolone, has been tried with some degree of success. In 1938, Deanesly and Parkes¹ reported the results of implantation into rabbits of progesterone tablets, 5.1 mg. in weight. Five days after the implantation, they found full progesterone effect in the uterus of the immature animal, which had previously been sensitized with estrone. They found the total absorption during the period was 1.5 mg. They suggested the clinical trial of implantation in cases of habitual abortion, where a steady, prolonged progesterone effect is desired.

During the past year, we have been gratified by the clinical results obtained with implantation of pellets of estrone in the treatment of the menopause. We found that a prolonged, continuous absorption of a small amount of hormone over a long period of time resulted from this method of therapy. It has been the observation of some clinicians² that in cases of habitual abortion, small doses of progesterone injected daily are more effective than large amounts administered once or twice a week. We decided to try the administration by implantation of progesterone tablets weighing 45 to 60 mg. in a group of cases in which

M. R., aged 20 years: Severe dysmenorrhea past five years. Examination essentially negative. Uterus normal by rectal examination. Menstrual history: onset eleven years, interval twenty-four days, duration two to four days. Implantation of 55 mg. of progesterone was done on Aug. 10, 1940. Menstrual history after implantation as follows:

Aug. 11, 1940, duration four days. Regular flow, severe pain.

Sept. 2, 1940, duration five days. Profuse flow. Slight cramps only for a few hours. No time lost from work, whereas previously patient lost one to two days.

Sept. 26, 1940, duration five days. Decreased flow, no pain.

Oct. 21, 1940, duration five days. Normal flow. Backache first day, but no pain.

R. R., aged 28 years: Primary dysmenorrhea. Examination: normal-sized uterus, freely movable. Right ovary enlarged to size of plum and tender. Menses: Onset at 14 years, irregular and prolonged intervals five to seven weeks, duration four to five days. First two days, moderate flow, then scant. Previous therapy: thyroid, gr. $\frac{1}{2}$, t. i. d. Biopsy taken on Aug. 30, 1940, the fifteenth day of the cycle, revealed a hypoplasia and slight proliferative activity. Biopsy taken on Sept. 5, 1940, the twentieth day of the cycle, showed an abortive secretory phase. Implantation was done Sept. 5, 1940, with 55 mg. of progesterone. Menstrual period

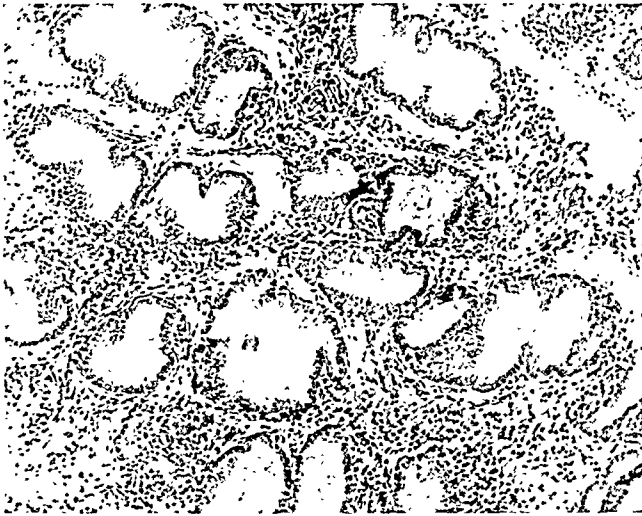


Fig. 3.—Primary dysmenorrhea (T. S.) (after therapy). Endometrial biopsy taken on twenty-third day of cycle. Well-developed secretory phase.

on Sept. 15, 1940, for five days. Patient stated: "This period began with less pain than I have ever known." Examination Oct. 7, 1940: right ovary normal in size. The following month patient experienced severe pain again. An additional implantation was done on Oct. 18, 1940, with 55.5 mg. of progesterone. Menstrual period began on October 22, duration four days. No pain with this period.

F. M., aged 30 years: Severe dysmenorrhea and premenstrual nausea. Examination: uterus normal. Basal metabolic rate -4 per cent. Menses: onset at 15 years, intervals four to seven weeks, duration eight days. Now flows only three days. Implantation of 47 mg. of progesterone on June 22, 1940. Menstrual history after implantation:

June 26, 1940, duration four days. Felt well, no pain. Best period since onset.

July 19, 1940, duration one day. No pain.

Aug. 17, 1940, duration two days. No pain or nausea.

Sept. 29, 1940, duration two days. Slight pain day before onset. Pellet practically absorbed.

O. M., aged 21 years: Severe dysmenorrhea. Rectal examination disclosed a small uterus. Menses: onset at age of 14 years, interval twenty-eight to thirty-four days, duration five to seven days. Previous therapy: preliminary course of estrone, 10,000 I. U. by injection three times weekly for two weeks. Implantation

Biopsy (Fig. 2) taken April 2, 1940, the twenty-fifth day of the cycle, showed slight evidence of secretion, dense stroma. Abortive secretory phase. Implantation of 56 mg. of progesterone was done on May 18, 1940. Menstrual period started twelve days later and lasted for seven days. There was increased flow and severe pain the first two days. On the fourth day of the period the progesterone pellet was spontaneously extruded. Second implantation, this time 49.5 mg. of progesterone was given on June 8, 1940. (Five days after extrusion of pellet.)

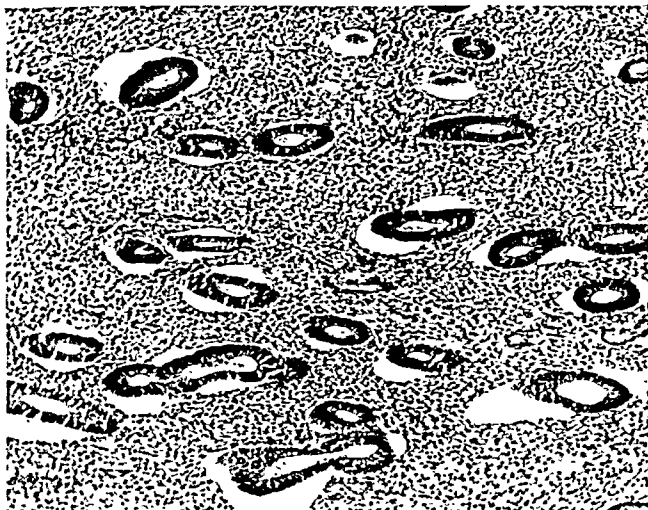


Fig. 1.—Primary dysmenorrhea (T. S.) (before therapy). Endometrial biopsy taken on eighteenth day of cycle. Moderate proliferation. No evidence of secretory phase.

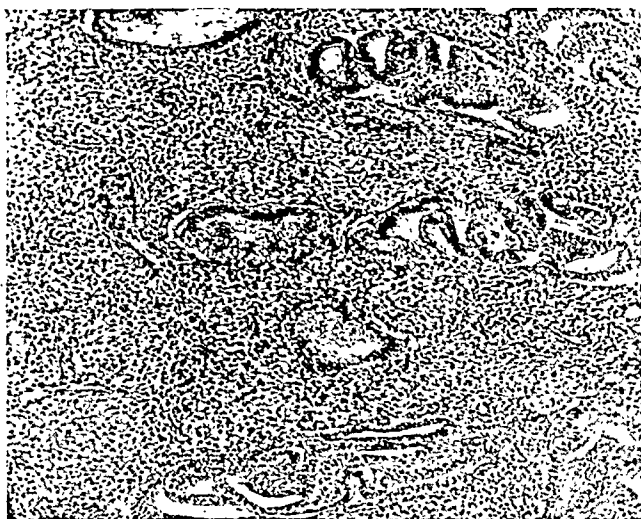


Fig. 2.—Primary dysmenorrhea (T. S.) (before therapy). Endometrial biopsy taken on twenty-fifth day of cycle. Slight evidence of secretion, dense stroma. Very little evidence of progesterone activity.

Menstrual history after reimplantation as follows:

July 8, 1940, duration eight days. No pain for the first time in two years.

Aug. 3, 1940, duration six days. Moderate flow, slight pain first day.

Sept. 8, 1940, duration seven days. Moderate discomfort second and third day.

Oct. 3, 1940, duration seven days. No pain.

Nov. 7, 1940, duration seven days. No pain.

Biopsy taken Sept. 30, 1940 (Fig. 3), the twenty-third day of the cycle, revealed a well-developed secretory phase with marked decidual reaction.

August 4, 1940, duration eight days, more profuse.

Biopsy taken July 3, 1940, on the twenty-fifth day of the cycle revealed a secretory phase.

A. W., aged 22 years: Menorrhagia, and metrorrhagia since delivery ten months ago. Menses: onset at 14 years of age, intervals two to three months, duration seven days. Previous therapy: Gonadotropic hormone 100 R. U. 3 times weekly. Bleeding September 2 to 11, using 12 to 15 pads daily. Biopsy taken on Sept. 7, 1940, showed an atrophy of the endometrium with irregularity of build. Implantation of 61.5 mg. of progesterone was done on Sept 7, 1940. Menstrual period

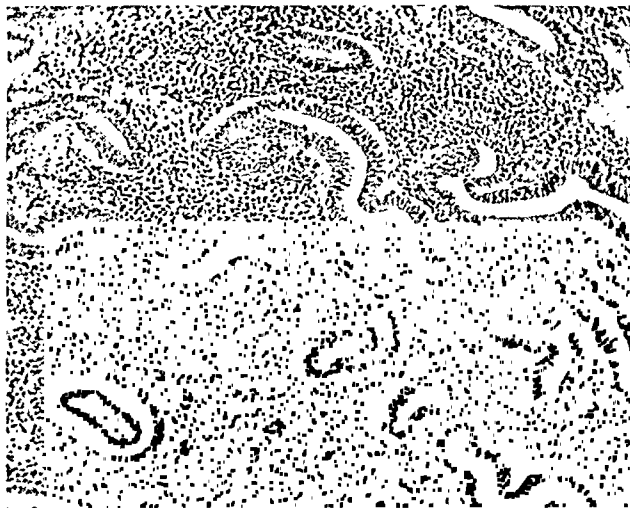


Fig. 4.—Functional bleeding (E. M.) (before therapy). Endometrial biopsy taken on twenty-seventh day of cycle. Marked proliferation. No evidence of secretion.

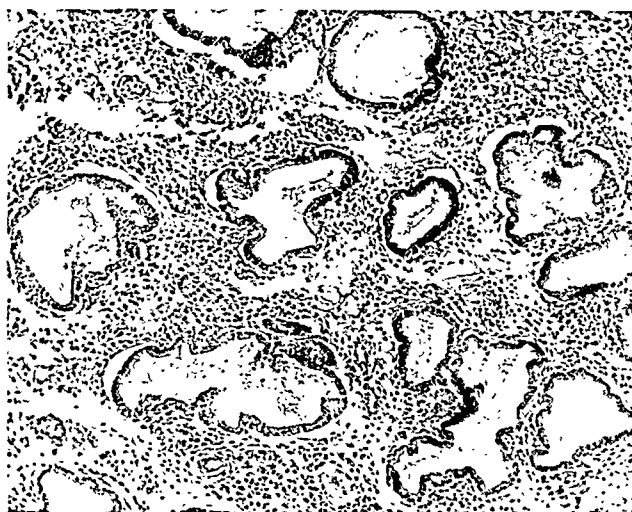


Fig. 5.—Functional bleeding (E. M.) (after therapy). Endometrial biopsy taken on twenty-fifth day of cycle. Functioning secretory endometrium.

September 22 to 27. On October 3, pellet extruded. Reimplantation with 56 mg. of progesterone on Oct. 5, 1940. Oct. 9, 1940, bleeding continued intermittently. Patient was referred for radiation therapy to pituitary gland.

DISCUSSION

Group I. Habitual and Threatened Abortion.—Of the 4 patients treated, one was delivered at full term. The second is now eight months

of 48.5 mg. of progesterone on June 10, 1940. Patient experienced premenstrual cramps on June 14. Menstrual history following implantation:

June 16, 1940, duration five days. Decreased flow, but less pain than any time since onset.

July 4, 1940, duration five days. Eighteen-day interval. Cramps first day.

Aug. 7, 1940, duration four days. Severe pain first day. Pellet extruded spontaneously.

Reimplantation with 49.5 mg. of progesterone on Aug. 19, 1940. Menstrual periods as follows:

Sept. 7, 1940, duration five days. Moderate cramps first day.

Oct. 14, 1940, duration six days. No pain, normal flow.

E. K., aged 18 years: Primary dysmenorrhea. Examination: uterus small. Basal metabolic rate $-6\frac{1}{2}$ per cent. Menses: onset at 14 years of age, interval twenty-eight days, duration four days. Previous therapy: estrone 10,000 I. U. three times weekly by injection. Implantation of 53 mg. of progesterone on Sept. 7, 1940. Menstrual history after implantation:

Sept. 13, 1940, duration four days. Severe pain at onset, but not as severe as before implantation.

Oct. 12, 1940, duration four days. Best period since onset. No pain, nausea, or vomiting. Patient still under observation.

GROUP III. FUNCTIONAL BLEEDING

E. M., aged 19 years: Menorrhagia. Menses: onset at $11\frac{1}{2}$ years of age, intervals three to four months, duration seven days, profuse flow. Past four months, periods prolonged two weeks' duration. Examination: eunuchoid type, span 67 inches, upper 30 inches, lower 37 inches. Basal metabolic rate -15 per cent. Hair and breasts normal. Biopsy (Fig. 4) taken on May 18, 1940, 27 days after onset of period shows a proliferative endometrium and physiologic hypertrophy. Implantation of 45.5 mg. of progesterone on June 1, 1940. Menstrual history following implant:

May 29, 1940 to June 5, 1940, June 24, 1940 to July 3, 1940, July 27, 1940 to Aug. 4, 1940, Aug. 24, 1940 to Aug. 31, 1940.

Normal flow each period.

Biopsy (Fig. 5) taken on the twenty-fifth day of the cycle, Aug. 21, 1940, reveals a functioning secretory phase.

A. G., aged 27 years: Menorrhagia. Menses: onset at 13 years of age, intervals four to seven weeks, duration seven days, profuse flow. Examination: bilateral cystic ovaries. Operation in November, 1939, partial resection bilateral cystic ovaries. Four months later, recurrence of symptoms as before. Biopsy taken in October, 1938, revealed an anovulatory endometrium. Biopsy taken in April, 1940, showed an abortive secretory phase with cystic glands. Implantation of 58.4 mg. of progesterone was done on May 16, 1940. Menstrual periods after implantation follow:

June 14, 1940, duration four days. Half in amount of period previous. Patient felt well.

July 16, 1940, pellet was spontaneously extruded. Since then periods have become as profuse as prior to therapy.

E. N., aged 28 years: Menorrhagia, metrorrhagia six months. Menses: onset at 13 years of age, interval twenty-eight days, duration four to five days. Examination revealed right ovary twice normal size. Basal metabolic rate $+15$ per cent. Biopsy taken on April 6, 1940, revealed a proliferative endometrium, mild local atrophy. Menstrual period April 15, 1940. Biopsy taken May 11, 1940, on the twenty-sixth day of the cycle, revealed an early proliferative phase; anovulatory endometrium. Implantation of 46 mg. of progesterone was done on June 1, 1940. Menstrual history following implantation:

June 13, 1940, less profuse, and no pain. Staining two days before onset, duration four days, no clots.

July 7, 1940, duration six days, regular in amount.

THE INCIDENCE OF ENDOMETRIAL HYPERPLASIA WITH UTERINE FIBROIDS AND EXTERNAL AND INTERNAL ENDOMETRIOSIS (ADENOMYOSIS)*

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TO INVESTIGATE the relationship of endometrial hyperplasia to uterine fibroids and endometriosis, we have reviewed the microscopic pattern of the endometrium in 727 uteri, containing one or more fibroid tumors, 108 cases of extrauterine endometriosis, and 82 cases of intrauterine endometriosis (adenomyosis).

The endometrium was classified as early or late proliferative, secretory, menstruating, pregnant, hyperplasia, and senile. Our diagnosis of endometrial hyperplasia is based on variation in size and shape of the endometrial glands, with large glands being characteristic. The glandular epithelium shows no evidence of secretion, the nuclei are large hyperchromatic, and mitotic figures are numerous. The stroma is compact and avascular. The individual stromal cells are small with hyperchromatic nuclei and scant cytoplasm. Mitotic figures are present but not as numerous as in the glandular epithelium. A normal endometrium of the late proliferative pattern presents many of these characteristics, and it is often difficult to decide in such endometria whether or not a diagnosis of hyperplasia should be made. It is admitted that some of the endometria classified as late proliferative might by others be classified as hyperplasia. The number, however, would not be large enough to alter materially our results.

ENDOMETRIAL HYPERPLASIA AND FIBROID TUMORS OF THE UTERUS

In a series of publications, Witherspoon¹ has emphasized the frequency with which he has found endometrial hyperplasia an accompanying pathologic condition of fibroid tumors of the uterus. He reached the hypothetical conclusion "that the unopposed action of estrin in the absence of corpus luteum influence if prolonged sufficiently would result in fibromyomatous growths." This conclusion was largely based on a 100 per cent incidence of endometrial hyperplasia in a series of 124 uteri which contained fibroid tumors and 26 cases of endometrial hyperplasia which later developed fibroids. This constant association of endometrial hyperplasia with uterine fibroid growths was at complete variance with our general impression of its frequency. A grouping of the 727 cases of uterine fibroids according to microscopic picture of the endometrium is presented in Table I.

*Read at the Fourth Annual Meeting of the Canadian Gynaecological Travel Society, Kingston, Ontario, October 26, 1940.

pregnant, and may thus be considered a successful result. The third, threatened abortion, is now three months pregnant, and is still under observation. The fourth is now six months gravid and is apparently a successful result. The results in this preliminary group of cases seemed to warrant prophylactic implantation with progesterone. This procedure was carried out in several cases of primary sterility where conception has taken place following x-ray stimulation to the pituitary and ovaries. It may be advisable to administer progesterone to any true sterility case as soon as conception has been definitely established in order to increase the capacity of the endometrium for nidation.

Group II. Dysmenorrhea.—Of the 6 cases reported, satisfactory results were obtained in 4 patients. These cases were observed for a period of three to six months, during which time the menstrual periods were almost entirely free of pain. In 3 cases, the pellets were extruded spontaneously after two to three weeks, but were retained upon reimplantation.

Group III. Functional Bleeding.—Clinical cures were obtained in 50 per cent of this small group of cases. In the successful cases, the endometrium showed a change from a persistent proliferative or abortive secretory phase to a well-developed secretory phase. These definite histological changes of the endometrium seem to indicate that the action of progesterone by implantation is effective. In one unsuccessful case (A. W.), a preliminary study of the endometrium showed no evidence of either estrone or progesterone activity. This case might have responded to progesterone, had we primed the endometrium beforehand with a sufficient amount of estrone, as it is well known that progesterone acts only upon an endometrium which has been stimulated previously by estrone. This fact is substantiated by evidence of estrone effect in the endometrium of our 2 successful cases, obtained before therapy was instituted. This emphasizes again the need for a complete endometrial study before institution of therapy.³

CONCLUSIONS

1. Satisfactory results were obtained in a small group of cases of habitual abortion, threatened abortion, and in cases of primary dysmenorrhea.

2. Satisfactory results were also obtained in 50 per cent of cases of functional bleeding.

3. As a result of these preliminary investigations, implantation therapy seems worthy of a further clinical trial.

I desire to thank Dr. Leon Motylloff, Pathologist to the Woman's Hospital, for the preparation and study of the endometrial specimens.

NOTE.—The progesterone pellets used in this study were pure synthetic alpha progesterone m.p. 128-130. The finely powdered material was compressed in a steel die punch tablet machine without addition of any inert diluent. The material was furnished through the courtesy of Dr. C. F. Longfellow of G. W. Carnrick Co., Newark, N. J.

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association of endometrial hyperplasia and external endometriosis. In our group of 108 specimens of endometriosis the results of microscopic examination of the endometrium of the uterine cavity were considerably different. These results are shown in Table II.

TABLE II. UTERINE ENDOMETRIAL PHASE IN 108 SPECIMENS OF EXTERNAL ENDOMETRIOSIS

Proliferative phase	34 cases	31.4%
Secretory phase	64 cases	59.2%
Hyperplasia phase	10 cases	9.2%

We have noted, however, that it is not unusual to have the ectopic endometrium fail to exhibit secretory change when the endometrium of the cavity is in the premenstrual phase. If the ectopic endometrium of endometriosis arises from serosa or germinal epithelium by heteroplasia, it is not surprising that in its varying stages of metaplasia and differentiation it shows an irregular and incomplete response to progesterone while it is dependent on estrin for its persistence and growth. The presence of a proliferative phase in such ectopic endometrium is not necessarily evidence of excessive estrin production. Endometrial hyperplasia of the uterine endometrium as evidence of prolonged or excessive estrin stimulation occurred in only 9.2 per cent of the 108 cases, an incidence not sufficiently high to warrant a conclusion that such a disturbance of estrin production is of etiologic significance in external endometriosis.

HYPERPLASIA AND UTERINE ENDOMETRIOSIS (ADENOMYOSIS)

Jeffcoate³ in 33 specimens of adenomyoma found hyperplasia of the uterine or ectopic endometrium in 29 cases despite the fact that 21 patients were operated upon during the premenstrual period. We have noticed a high incidence of the hyperplasia pattern in the ectopic endometrium of adenomyoma. This endometrium arises from the basal layer of the endometrium of the cavity which normally is of the hyperplasia pattern. The basal layer of the endometrium frequently fails to exhibit secretory manifestations during the premenstrual phase and can be often identified in early decidua. Hyperplasia of the endometrium in the adenomyomatous areas is not, in our opinion, evidence of excessive or prolonged estrin effect. We have noted, however, a relatively high incidence of hyperplasia of the uterine mucosa in adenomyosis. The results of the examination of the endometrium in 82 specimens are shown in Table III.

TABLE III. UTERINE ENDOMETRIAL PHASE IN 82 SPECIMENS OF UTERINE ENDOMETRIOSIS

Secretory phase	39 cases	47.5%
Proliferative phase	23 cases	28.1%
Hyperplasia	20 cases	24.3%
Total	82 cases	99.9%

TABLE I

Proliferative phase		274 cases	37.7%
Early	34 cases		
Late	240 cases		
Secretory phase		385 cases	53.0%
Premenstrual	267		
Menstrual	83		
Pregnant	35		
Hyperplasia		50 cases	6.5%
Senile		18 cases	2.4%
Total		727 cases	99.6%

The findings are about what we expected, a slightly higher incidence in the secretory phase group, due to the frequency with which hysterectomy has to be performed during menstruation and the immediate premenstrual period when fibroids are a cause of menorrhagia.

The physiologic action of estrin on the myometrium makes it a reasonable assumption that the growth of uterine fibroids, in part at least, is dependent on estrin stimulation. The age incidence of fibroid tumors, their characteristic rapid growth during pregnancy and atrophy after cessation of ovarian activity are clinical evidence of such dependency, but not evidence that disturbed estrin production is of etiologic importance in their origin. Myometrial hypertrophy is not a constant finding with uterine fibroids, and menstrual disturbances are usually gradual in onset and occur most commonly when submucous tumors are present. It is surprising how often menstruation is undisturbed even when quite large fibroids are present in the uterus. In a clinical analysis of 100 consecutive cases of complicated and uncomplicated uterine fibroids operated upon on our service, menstruation was normal in 43 cases.

In this group of 727 cases of uterine fibroids, endometrial hyperplasia, as evidence of prolonged unopposed or excessive estrin stimulation, did not occur with sufficient frequency to justify a conclusion that such a disturbance of estrin production plays any role in the origin of uterine fibroids.

HYPERPLASIA AND ENDOMETRIOSIS (EXTRAUTERINE)

Smith,² Jeffcoate,³ and Witherspoon⁴ have drawn attention to the frequency with which they have found endometriosis and hyperplasia as associated conditions. G. V. Smith reported 42 per cent of his cases of endometriosis complicated by "gland hypertrophy." Jeffcoate in 78 cases of external endometriosis stated "that the uterine endometrium showed hyperplasia or other features dependent on excessive estrin stimulation in all specimens examined." He concluded "that the development of endometriosis irrespective of the primary source of the endometrial elements is due to excessive estrin production by the ovaries." On the other hand, Fallas and Rosenblum⁵ reported 10.7 per cent incidence of endometrial hyperplasia in 260 cases of internal and external endometriosis. We have not been impressed with the frequent

tachysterol (A.T.10*). To our knowledge, she was the first pregnant woman so treated. A detailed account of this case prior to the pregnancy has been reported by J. K. Curtis.⁴

Chemically, A.T.10 is a derivative of irradiated ergosterin. The fraction, tachysterin, is converted to dihydrotachysterol to make it suitable for administration by mouth. This drug is potent in increasing calcium absorption from the intestines and raising the blood calcium level. It has been found very useful in managing cases of hypoparathyroidism.

CASE REPORT

The patient, B. M., a 15-year-old schoolgirl was first seen at the First Surgical Division of Bellevue Hospital in March, 1931. She had typical signs and symptoms of hyperthyroidism. After the usual preparation a subtotal thyroidectomy was performed. The patient improved, but after a few months there was a recurrence of her old complaints. Another partial thyroidectomy was performed, and she was again discharged improved.

The patient then married. In 1936 she was delivered of a normal full-term infant without difficulty. In spite of taking iodine intermittently she returned to the hospital in 1937 with a recurrence of her symptoms of hyperthyroidism. A third partial thyroidectomy was performed. No parathyroid tissue was noted grossly or microscopically in the removed specimen.

Two days postoperatively the patient complained of stiffness in the fingers and muscle cramps. Chvostek and Trousseau's signs were present. She received all the usual forms of treatment of tetany, including high calcium, low phosphorus, and ketogenic diets; calcium orally and intravenously; viosterol and parathormone. In spite of this therapy she had several severe convulsions. In April, 1937, four months after her last operation, blood partition showed: calcium, 5.7 mg. per cent; inorganic phosphorus, 5.5 mg. per cent; serum phosphatase, 3.1 Bodansky units; nonprotein nitrogen, 28 mg. per cent; total protein, 8; albumin, 4.8; globulin, 3.2; euglobulin, 0.7. A year later blood calcium was 4.8; phosphorus, 5.8 (see Table I).

The patient went one year and nine months in a profound degree of parathyroid insufficiency, unrelieved by the customary forms of therapy. At this point anti-tetanic 10 was given, the patient receiving 1 c.c., along with 2 teaspoonfuls of calcium lactate and 20 drops of viosterol daily. In a week she was much improved. She gained weight, had no complaints, and Chvostek and Trousseau's signs were absent. In April, 1939, blood calcium was 9.9; phosphorus, 4.6. Since the blood

TABLE I. SHOWS WEIGHT, BLOOD CHEMISTRY DETERMINATIONS, AND THERAPY IN A PATIENT WITH HYPOPARATHYROIDISM BEFORE PREGNANCY

DATE	WEIGHT POUNDS	MEDICATION			BLOOD CHEMISTRY			
		CA. LAC- TATE GR.	VIO- STEROL GTT.	A.T.10 C.C.	CA.	P.	PHOS- PHA- TASE	N.P.N.
4/19/37	122	25	30		5.7	5.5	3.1	28
3/30/38	115½	25	30					
10/19/38	110¾	10	20	1.0	4.8	5.8		
11/ 2/38	112	10	20	1.0				
11/ 9/38	113½	10	20	1.0				
11/23/38	114½	10	20	1.0				
12/21/38		10	20	1.0	7.0			
3/ 1/39	115¾	10	20	1.0	9.9	4.6	0.9	33
4/18/39	117½	10	20					
5/ 3/ 39	116	10	20	1.0	5.5	5.6		
5/31/39	115	10	20	0.5				

*Abbreviation for "anti-tetanic 10," prepared by Winthrop Chemical Co., N. Y.

This 25 per cent incidence of hyperplasia is significant. The basal layer of the endometrium normally exhibits a rather uneven junction with the myometrium and frequently shows a tendency to dip down in a superficial manner between the muscle bundles. With endometrial hyperplasia it would seem reasonable to assume that this tendency might be exaggerated, even to the point of producing a typical adenomyoma.

SUMMARY

Endometrial hyperplasia of the Schroeder or "Swiss cheese type" occurred in 6.5 per cent of 727 uteri, containing one or more fibroid tumors. It occurred in 9.2 per cent of the uterine endometrium in 108 cases of external endometriosis. Endometrial hyperplasia as evidence of prolonged, excessive, or unopposed action of estrin did not occur with sufficient frequency in either group of cases to warrant a conclusion that such a disturbance of estrin production is of etiologic significance in their origin.

The occurrence of endometrial hyperplasia in the endometrium of the cavity of the uterus in 25 per cent of 82 cases of adenomyosis suggests that a disturbance of estrin production may be of etiologic importance in this condition.

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HYPOPARATHYROIDISM IN PREGNANCY, TREATED WITH DIHYDROTACHYSTEROL

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TETANY rarely occurs in the course of pregnancy, and parathyroid deficiency is usually postulated as its cause. According to Hartley,¹ "latent tetany" often occurs during pregnancy and reveals itself by paresthesias, insomnia, edema, and cramplike pains in the legs and thighs. Both tetany and "latent tetany," as Shelling² has aptly stated, may not be due to parathyroid insufficiency, but to several other factors, "such as the calcium and phosphorous, and vitamin D intake, and the calcium and phosphorous storage." Although 54 cases of tetany in pregnancy could be found in the literature, in only one case was the tetany preceded by an operation in which the parathyroids had been removed or damaged. This case was reported by Baumgartner and Cowles.³ The tetany followed two months after a subtotal thyroidectomy for hyperthyroidism. The patient was treated with calcium, cod-liver oil, and parathormone, but later the parathormone was discontinued. She subsequently delivered a normal term infant. The writers wish to report a similar case. Our patient, however, was carried through her pregnancy with the help of dihydro-

calcium was a little high (10.7 mg. per cent), the dosage of anti-tetanic 10 was reduced from 1 c.c. t.i.d. to 1 c.c. b.i.d. daily (see Table II). The puerperium was non-morbid and uneventful. On the tenth post-partum day she was sterilized by the technique of Pomeroy through a small abdominal incision. The postoperative course was smooth. The patient was discharged with her infant on the twenty-second post-partum and thirteenth postoperative day, both in good condition. X-ray of the long bones of both mother and infant showed no abnormalities.

SUMMARY

A case is reported of chronic parathyroidism following a subtotal thyroidectomy, in which the blood calcium was maintained at normal levels by the use of anti-tetanic 10 (dihydrotachysterol) along with calcium and viosterol. The patient subsequently became pregnant. The pregnancy, delivery, and puerperium were uneventful. To our knowledge, this is the only pregnancy in which anti-tetanic 10 has been used.

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ADEQUATE TRANSVAGINAL DRAINAGE OF THE PELVIS

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THE technique for excision of diseased female generative organs has been constantly improved, yet methods for draining the pelvis after operation have not kept pace with these advances. The common causes of morbidity and mortality following hysterectomy are complications arising in the pelvic peritoneal cavity. The most frequent complications are peritonitis, abscess, hematoma, and intestinal obstruction. Inadequate postoperative drainage of the pelvis is the factor which precedes and predisposes to these unfortunate post-operative conditions.

Gynecologists, in general, acknowledge the highest mortality from panhysterectomy, a lower mortality from supravaginal hysterectomy, and the lowest mortality from vaginal hysterectomy.¹⁻⁵ It does not seem rational that the majority of operators should prefer the abdominal approach for excision of the uterus when the lowest mortality is obtained from transvaginal operations, yet this is apparently the case. There is one striking difference in the various techniques for excision of the uterus which accounts for the minimum mortality rate from vaginal hysterectomy. This is the excellent facility for release of bloody serum from the pelvis through a vent in the vaginal vault after operation. Strangely enough, vaginal hysterectomy which reports the lowest mortality rate also reports the highest morbidity rate.^{1, 5, 6} The obvious reason for this is failure to obtain adequate drainage through the vaginal vault after operation.

The most frequent cause of death following hysterectomy is peritonitis.^{1, 2, 5, 7} If the peritoneal cavity can be adequately drained of the free fluid which forms after operation, spreading peritonitis can be largely prevented, because peritonitis spreads by means of a liquid medium. Bloody serum which collects in the pelvis after hysterectomy acts as an ideal pabulum for pathogenic bacteria introduced at the time of operation. True, our aseptic methods for the abdominal operation will hold contamination at a minimum, but in transvaginal operations the contamination is undoubtedly much greater, since the cervix and vaginal mucosa cannot be made sterile. Patients who are not required to absorb either sterile or septic fluid from the peritoneal cavity after operation will have a lower morbidity and mortality rate, a lower incidence of postoperative ileus, a smoother convalescence, and a shorter hospitalization period.

calcium was now normal, the anti-tetanic 10 was discontinued in the hope that a normal calcium level could be maintained by giving only calcium lactate and viosterol. The blood calcium, however, promptly dropped, and her old complaints returned. Her symptoms again disappeared after receiving antitetanic 10. Her maintenance dose appeared to be 1 c.c. daily, and she continued to receive this amount (see Table I).

When seen in October, 1939, at the Bellevue Obstetrical Clinic, she was two and one-half months pregnant. Therapeutic abortion was considered, but because of her good general physical condition and intense desire for another child, the pregnancy was not interrupted. The blood calcium was taken at frequent intervals, and she was closely followed throughout her pregnancy. In order to maintain a normal blood calcium, the maintenance dose of anti-tetanic 10 was gradually increased from 1 c.c. daily to 1 c.c. t.i.d. She also received 15 gr. of calcium lactate t.i.d. and 10 minims of viosterol b.i.d. (see Table II). The patient felt well throughout her pregnancy and offered no complaints.

TABLE II. SHOWS WEIGHT, BLOOD CHEMISTRY DETERMINATIONS, AND THERAPY IN A PATIENT WITH HYPOPARATHYROIDISM DURING HER PREGNANCY AND PUERPERIUM

DATE	WEIGHT POUNDS	MEDICATION			BLOOD CHEMISTRY			
		CA. LACTATE GR.	VIO- TEROL GTT.	A.T.10 C.C.	CA.	P.	PHOS- PHATASE	N.P.N.
9/27/39	117½	10	10 o.d.	2	6.2	5.4		
10/18/39	114½	10	10 o.d.	1	8.5	4.3		
11/22/39	116¾	10	20 o.d.	2				
12/13/39	118½	30	20 o.d.	3				
12/20/39	120	45	20 b.i.d.	3				
1/ 3/40	121¼	45	20 b.i.d.	3				
1/10/40	122½	45	20 b.i.d.	3	9.8			
1/24/40	123½	45	20 b.i.d.	3				
2/ 7/40	125¾	45	20 b.i.d.	3				
2/21/40	126½	45	20 b.i.d.	3				
3/ 6/40	128¾	45	20 b.i.d.	3				
3/20/40	128	45	20 b.i.d.	3	9.1	4.1		27
4/ 3/40	130	45	20 b.i.d.	3				
4/17/40	133	45	20 b.i.d.	3	9.4	4.6	7.0	36
5/ 1/40	138	45	20 b.i.d.	3				
5/15/40	134	45	20 b.i.d.	3	9.0		9.0	29
5/29/40	15 gr. cal- cium glu- conate I V							
Birth of Infant								
6/ 3/40		30	15 b.i.d.	2	10.7		4.6	
7/ 3/40	116½	15	10 b.i.d.	½				
7/31/40	113½	15	10 b.i.d.	½				
9/18/40	112	15	10 b.i.d.	½				

She was admitted to the obstetric ward at midnight of May 29, 1940. Labor pains had started a few hours before admission. The patient was now in active labor. A slightly oversized full-term infant was presenting by the breech, which was at the level of the spines. The cervix was fully dilated. Physical examination was otherwise essentially negative. Soon after admission the infant was easily delivered as an assisted breech and was an apparently normal female child, weighing 8 pounds and measuring 20 inches in length. The third stage of labor was uneventful, and immediately following this the patient received 10 c.c. of 10 per cent calcium gluconate intravenously. Both mother and infant were returned to the ward in good condition. She ran a non-morbid, uneventful post-partum course. She was not allowed to nurse the infant. On the fourth post-partum day, because the blood

Any technique for excision of the uterus may be employed, but the opening in the vaginal vault after vaginal hysterectomy should then be partly closed to leave a fenestration of appropriate diameter to fit around the glass tube. The vaginal walls are protected from pressure of the glass drain by a strip of plain gauze packing which is moistened with saline and inserted loosely around the tube from the vaginal vault to the introitus. No gauze is introduced into the pelvic opening (Fig. 2). The drainage of serous fluid is frequently so profuse during the first and second postoperative days that the perineal pads become saturated and wet the bedding unless replaced every few hours. I do not know of any convenient method for estimating the amount of drainage in these cases, but to even the casual observer there is considerably more fluid from the glass tube drain than is seen when gauze or rubber drains are used.

Drainage is usually scanty by the third postoperative day, and it has been routine to remove the glass tube at that time. The patient is placed on an examining table, the vaginal gauze packing gently withdrawn, the anchoring suture cut, and the glass tube which does not stick to the tissues is easily slipped out. A bivalve speculum is then inserted and a view through the opening in the vault reveals a normal glistening peritoneum without exudate or adhesions. With the speculum in place, the vagina is again loosely packed with saline moistened gauze from vault to introitus. Gauze is never introduced through the opening into the pelvis.

Vaginal packing is removed without difficulty on the fifth or sixth postoperative day. By this time the opening into the pelvis is already sealed off and healing progresses rapidly. The patient is permitted out of bed on the seventh to ninth day after operation.

This procedure for pelvic drainage has been employed in a small series of vaginal hysterectomies. Technique of excision was the serial suture-ligation and division of vessels without clamps.⁹ Annealed stainless steel wire was used for all ligatures and sutures in preference to catgut or silk which produce unfavorable foreign protein reactions in tissue.¹⁰

Table I summarizes the data on fifteen consecutive hysterectomies treated with the transvaginal pelvic glass tube drain. Indications for operation were procidentia uteri, fibrosis uteri, and fibroid tumors. One-third of the patients had large tumor masses palpable by abdominal examination. These varied in size up to the dimensions of a five months' pregnancy and required morcellation for removal. Nearly

TABLE I. SUMMARY OF 15 CONSECUTIVE VAGINAL HYSTERECTOMIES TREATED WITH THE TRANSVAGINAL GLASS TUBE DRAIN

Age range	27-63 years
Average age	42 years
Anesthesia:	
Spinal	93%
Local	7%
Excision by morcellation	33%
Other operations + hysterectomy	46%
Average postoperative days in hospital	10 days
Postoperative morbidity	Pyelitis, 1 case

one-half of the group underwent other operations at the time of hysterectomy, including oophorectomy, salpingectomy, posterior colpoperineoplasty, and repair of abdominal incisional hernia. One patient developed a transient pyelitis after operation. This was the only case with postoperative morbidity and none of the others had a temperature above 100.6° F. for any twenty-four-hour period. All of the patients were comfortable after operation and none complained of discomfort from the glass drainage tube. One patient, 27 years old, who was operated for third degree procidentia uteri with a two months' pregnancy and recurrent uterine hemorrhages, was allowed out of bed on the fifth day after operation and returned home on the sixth day in good condition. Although there was no

Rubber or gauze should not be placed in the peritoneal cavity when free drainage is desired. Laboratory and clinical observations have shown that these substances produce a marked local irritation of the peritoneum.⁸ This results in a rapid fibroplastic exudative incapsulation of the rubber and gauze. Within six to eight hours the reaction of the peritoneum to rubber or gauze converts these drains into mechanical corks which actually impede the escape of septic fluids and are effectual in draining only the limited tissue space which they irritate. Drains made of inorganic materials such as glass or stainless steel produce little or no irritation of the peritoneum and, therefore, afford a satisfactory material for obtaining prolonged and adequate drainage.

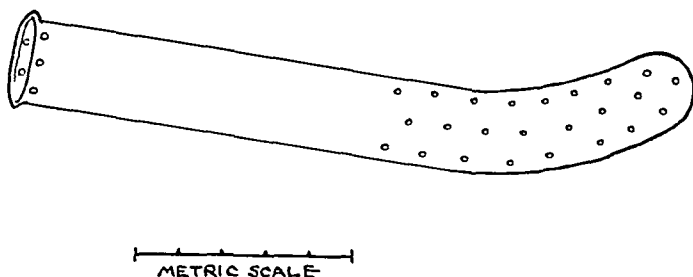


Fig. 1.—Pyrex glass tube which is inserted into the pelvis through the vaginal vault to drain the peritoneal cavity for three days following hysterectomy.

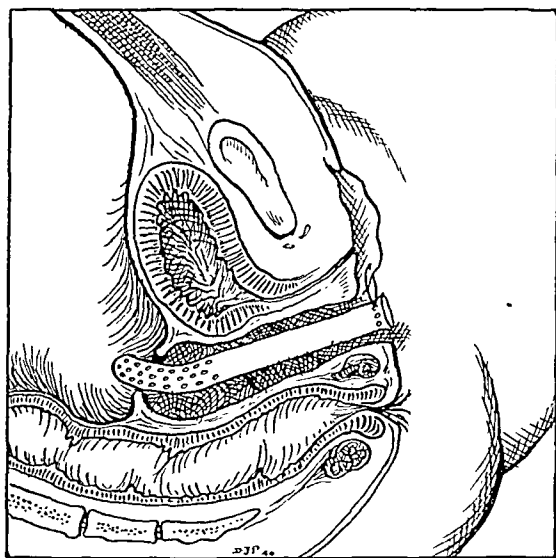


Fig. 2.—Diagram in the sagittal plane, showing position of glass tube for prolonged gravity drainage of the pelvis after excision of the uterus. Gauze or rubber inserted into the pelvis prevents adequate free drainage.

By substituting a non-irritating drain made of inorganic material for the gauze or rubber drains commonly in use, one can obtain free drainage from the pelvis after vaginal hysterectomy. It is ineffectual and dangerous to leave an unprotected opening in the vaginal vault after operation, as the hole would be quickly plugged by an intestinal loop and lead to the possibility of intestinal herniation. A suitable glass tube (Fig. 1) introduced into the pelvis prevents hernia and maintains prolonged open drainage. This type of tube is made of pyrex glass and can be constructed according to specifications by a glass blower. It may be curved to conform to the shape of the pelvic passage. The end which is inserted into the pelvis is rounded and closed but contains multiple small perforations 1 to 2 mm. in diameter. The external end is open and may be anchored to the labia by a suture through one of the small holes along the rim.

BILATERAL GRANULOSA CELL TUMORS*

SUCCESSFUL REMOVAL FROM A CHILD FOURTEEN WEEKS OF AGE

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INTEREST in solid ovarian tumors has been greatly stimulated in the past few years as a result of correlation between the known histologic structure of such tumors and the more modern methods of identifying their hormonal content. To Rokitansky perhaps belongs the credit for first describing a tumor composed mainly of large and small follicular structures surrounding protoplasmic disks filled with granular bodies. Pathologists who amplified his description were Acconci, von Kahlden, Schroeder, Werdt, and Meyer.

In spite of much investigation, little is known of the origin of these tumors. Among the many concepts is that of Meyer, who felt that the tumors arose from cell rests in the ovarian hilus. Recent experiments of Butterworth have tended to show that the growths might be produced experimentally as a result of roentgen therapy. If this concept is sustained, an intimate relationship between the development of such tumors and the application of roentgen therapy to women may be established. The evidence for such a relationship, however, is as yet inconclusive.

Robinson, in 1923, was the first to publish in the American literature a report of a case of granulosa cell tumor. King, in 1929, reported 2 cases, and since 1930 the number of reports of cases has increased to considerably more than 400. Among the prominent contributors to the subject might be mentioned Novak, Long, TeLinde, Frank, Schulze and Neumann. One of the most comprehensive reviews of the subject of granulosa cell tumors was reported in 1935 by Bland and Goldstein. At that time 160 cases of this type of tumor were recorded. In 1939, Dockerty and MacCarthy added 30 cases from material gathered at the Clinic from 1905 to 1937.

Study of the data on granulosa cell tumors so far reported brings out certain definite clinical characteristics of this tumor. Sixty per cent of granulosa cell tumors occur after the menopause and 30 per cent between puberty and the climacteric, whereas only 5 to 10 per cent occur before adolescence. The relatively infrequent occurrence of this type of tumor before adolescence is indicated by the fact that only eight tumors occurred among patients less than twelve years of age in the series of 160 reports of cases collected by Bland and Goldstein. The respective ages of these patients, in years, was 5, 9, 5, 11½, 4, 5, 6, and 7. The youngest patient represented in the foregoing series, and probably in the literature up to the time of writing the present article, was 4 years of age; the case was reported by Novak. The matter of age is of some significance, since we believe our patient to be the youngest individual in relation to whom a granulosa cell tumor has been diagnosed and from whom such a tumor has been successfully removed. The tumors in this case were bilateral, although such tumors occur bilaterally in less than 5 per cent of cases. When, therefore, the fact is considered that only 20 per cent of all ovarian tumors are solid and that of these only 10 per cent are granulosa cell tumors, this case becomes almost a medical curiosity.

In childhood it is not uncommon for precocious menstruation, together with early sexual and somatic development, to be a symptom of these tumors. However, these need not be leading symptoms. Additional presenting symptoms may include abdominal tumor, abdominal pain, ascites, or hypertrichosis. The tumor may even be discovered accidentally. The present case is further interesting, since the only suggestion of the presence of disease was abdominal tumor.

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apparent harm from her early return to activity, it would seem wise to keep these patients in bed for at least seven days. The average postoperative period of convalescence in the hospital for this group was ten days.

It is not the purpose of this article to advocate vaginal hysterectomy as being better than operations done through an abdominal incision. However, it is the purpose here to indicate the advantages of glass tube gravity drainage of the pelvis following excision of the uterus. It is rational to believe that the higher death rate from supravaginal hysterectomy could be reduced to a figure approaching the present mortality rate for vaginal hysterectomy if the principles of adequate pelvic drainage were applied. For this reason it is suggested that following the abdominal closure in supravaginal hysterectomy, the patient should be draped in the lithotomy position, an opening made in the posterior vaginal cul-de-sac and a transvaginal glass tube drain inserted into the pelvis to complete the operation. This will afford prolonged free gravity drainage which cannot be secured with gauze or rubber drains whether they be inserted through an abdominal incision or through the vaginal cul-de-sac. The disability and death from peritonitis, abscess, hematoma, and intestinal obstruction can be largely prevented if adequate drainage of the pelvis is maintained during the early days after hysterectomy. Although the method here described has been used for only a short time, the favorable results obtained indicate that further use of this new technique for drainage is warranted.

SUMMARY

The advantages of the transvaginal glass tube pelvic drain following hysterectomy are:

1. The special glass tube affords adequate and prolonged gravity drainage of the pelvic peritoneal cavity which cannot be obtained by the use of gauze or rubber drains.
2. Septic or spreading peritonitis is prevented by removal of all free fluid from the pelvis which may act as a culture medium for bacteria and a vector for transmitting infection into the abdominal cavity.
3. Intestinal obstruction after operation is prevented by free drainage through the glass tube of septic materials which result in plastic exudate and peritoneal adhesions. Gauze and rubber, because of their organic composition, produce irritation resulting in fibroplastic exudate and should not be introduced into the peritoneal cavity.
4. Immediate recognition of secondary hemorrhage after hysterectomy may be life-saving. Hemorrhage from a slipping ligature becomes apparent at once, since the open glass drain gives rapid egress for blood from the pelvis and thereby prevents unrecognized hemoperitoneum.
5. The glass drain does not stick to the tissues and can be removed easily without trauma. Foreign body irritation of the peritoneum is reduced to a minimum, since the inorganic glass tube produces little or no tissue reaction.
6. Reduction of postoperative morbidity from intrapelvic complications results in a shorter period of hospitalization. Adequate prolonged drainage of the pelvis from the time of operation prevents the formation of abscess and hematoma.
7. Excision of the uterus by any technique or method does not preclude the use of the transvaginal glass tube drain, nor does this tube interdict vaginal plastic or perineal operations in conjunction with hysterectomy.

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In spite of the diagnosis of abdominal malignancy, exploration was made by one of us (Zemke) on July 23, with the patient under ether anesthesia. The child was then sixteen weeks of age. Bilateral, solid ovarian tumors were found (Fig. 1 *a*, *b*, and *c*). The uterus was considered to be of average infantile size although it may have been slightly enlarged. Bilateral oophorectomy was performed, leaving the uterus and other adnexa intact. The wound was closed in the usual manner. Postoperative convalescence was uneventful and the girl was dismissed from the hospital on the seventh postoperative day.

From that time onward, the child made what might be considered normal progress. She was seen at intervals of about three months. Eleven months from the time of operation the child's weight was 23 pounds 9 ounces (10.7 kg.), which represents a gain of approximately 13 pounds (almost 6 kg.) in less than a year.

Up to this time, the child herself had not been seen by a physician of the Mayo Clinic, but in May, 1940, one of us (Herrell), in informal conversation concerning the case, suspected the growths of being granulosa cell tumors and, a few days later, was able to confirm the suspicion by gross and microscopic examination of the tissue. Characteristic cells, with large basophilic nuclei, constituted the predominant cellular structure. The structural unit also was characteristically cylindroid with transitions to the folliculoid type (Fig. 2 *a* and *b*). Grossly, both tumors were well



Fig. 3.—Appearance of patient. Ages from left to right: seven and one-half, sixteen, and thirty-three months.

encapsulated; their surfaces were smooth and grayish brown. On section, the masses were solid throughout and were of homogeneous, granular texture. The diagnosis of granulosa cell tumor was further confirmed by Dockerty of the Mayo Foundation of the University of Minnesota, at Rochester, and it was subsequently learned that Bell, of the same university, in Minneapolis, in the light of the subsequent clinical course, had suspected the true nature of the tumors.

The child's growth and development were entirely within normal limits and, at the time of writing this report, she had been followed for three years and two months (thirty-eight months) (Fig. 3). When last seen Sept. 1, 1940, she enjoyed perfect health. Her height at that time was 37 inches (93.94 cm.) and her weight, 33 pounds (15.0 kg.).

Endometrial studies were not possible and, unfortunately, studies with relation to urinary or blood hormonal content were not available. The specimens also were preserved in formalin, which precluded their study from the standpoint of hormonal content.

SUMMARY

Bilateral tumors of the ovaries were discovered when the child was fourteen weeks of age, and the tumors were successfully removed when she was sixteen weeks of age. Two years and eight months later these tumors were determined to be

REPORT OF CASE

A white American girl was born uneventfully, at full term, April 1, 1937. The mother had had one child previously. The birth weight of the child was 8 pounds 13 ounces (4 kg.). Her early progress was satisfactory except that she did not gain weight normally. On May 19, when the child was examined because of a feeding problem, her weight was 10 pounds (4.5 kg.); she had gained only 1 pound 3 ounces (0.6 kg.) since birth. Alteration in the child's formula was prescribed. She was seen again on June 1, at which time she had gained only 1½ ounces (45 Gm.) more than the weight noted on the visit on May 19, in spite of what might be considered an increase in feeding.

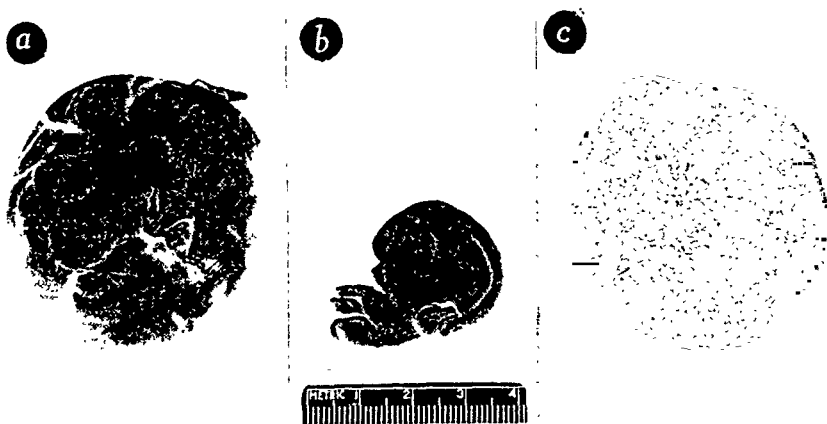


Fig. 1.—Bilateral granulosa cell tumors: *a*, tumor from right side, 5 by 5 by 4 cm.; *b*, tumor from left side, 3 by 2.5 by 2 cm.; *c*, cut surface of the larger tumor.

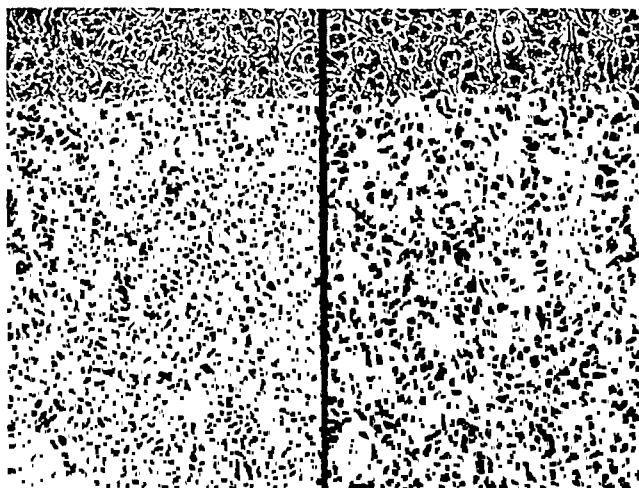


Fig. 2.—Different section of tumor stained with hematoxylin and eosin: *a*, cylindroid and diffuse cellular pattern ($\times 140$); *b*, folliculoid cellular pattern ($\times 200$).

The child was seen once more on July 9. She was then fourteen weeks of age and her weight was 10 pounds 10 ounces (4.8 kg.), which represents a gain over the original birth weight of only 1 pound 13 ounces (almost 1 kg.). At this time, a mass was found in the lower right abdominal quadrant. This mass, which was the size of a large lemon, had not been present when previous examinations had been made. The remainder of the examination did not disclose anything abnormal. Consultation was then sought concerning the tumor. The diagnosis entertained by all the consulting physicians was a malignant growth involving either a kidney or an ovary, and the prognosis was considered grave.

Grant,⁵ in 1921, reviewed the classification of double monsters and reported a case. The mother was a primipara, aged 28 years. The delivery was difficult but spontaneous. X-ray study revealed a dicephalic monster with double spine and a clavicle between the two heads.

In 1926, Ivens and Edgecombe⁶ reported a case of dicephalus dibroachius dipus causing obstructed labor. The specimen was a double-headed monster weighing about seven pounds. There were two heads, two arms, two legs, and a single body which had two distinct spinal columns, approximating in the sacral region.

Mandrizzato,⁷ in 1932, published a detailed article on the embryogenesis of anencephalia and spina bifida. This article is included in the review of cases because of his studies of spina bifida, an anomaly in the case being reported.

Rose,⁸ Morrison,⁹ and Mitchell¹⁰ in 1927, reported three dicephalic monsters. The first was a dicephalic fetus with apparently normal body. The second was a similar case, both of which were exceedingly difficult deliveries. The third case was of a different type, being a syncephalus thoracopagus. There were four arms and four legs, the bodies being united at the thorax.

In 1931, Shortall¹¹ reported a case of double monster occurring in a secundipara, aged 33 years. Examination of the specimen disclosed two female fetuses fused at the pelvis, anteriorly. Radiologic examination revealed a fusion of the lumbosacral region of the vertebral columns with absence of one sacrum.

Mudaliar,¹² in 1931, reviewed double monsters in an extensive study of their circulatory system and some other anatomic abnormalities and the complications in labor. His radiographic studies and drawings are most complete and enlightening to one interested in these embryologic anomalies.

REPORT OF AUTHOR'S CASE

The patient, a secundipara, was 28 years of age. Her previous pregnancy was a normal one at the age of 25. Her prepartum course in the first pregnancy was normal in every respect. The baby, a female, weighed 8 pounds 1 ounce at birth and the delivery was spontaneous. Her post-partum course was entirely normal and satisfactory.

She presented herself to her physician with this pregnancy when she had missed her second period. Her routine physical examination at that time was negative except for some tenderness under the right costal margin in the region of the gall bladder. She was given routine prenatal care every three weeks, i.e., urinalysis, weight, blood pressure, and fundal measurement. When she was about six and one-half months pregnant, it was noted that there had been a sudden rise in the fundal measurement and the fetal heart could no longer be heard. It was impossible to palpate fetal outlines so a diagnosis of polyhydramnios was made. In view of the fact that there was a possibility of multiple pregnancy or monster, a routine x-ray study of the patient was advised. This was performed at the seventh month, at which time her fundal measurement had risen to 33 cm. (term size). The roentgenologist's report on that study, done on May 14, 1940, by George U. Pillmore, M.D., Roentgenologist at the Easton Hospital, follows:

Roentgenologist's Report.—"The x-ray examination of the abdomen discloses a teratologic specimen of the anencephalic type developed well along toward full term. There is a mid curvature of the spine, and it is noted that the rib spacing is rather close together on one side. Possibilities exist as to the presence of an extra vertebra causing the distortion of the spine or it may be because of collapse of the chest commonly seen at fetal death. Request the privilege of x-ray and photographing specimen after delivery."

When the report was studied by the roentgenologist and myself, the family was advised that the child would be a nonviable monster, and they were advised that the pregnancy would best be allowed to terminate spontaneously.

During the next month, the fundal measurement rose to 39 cm. and the patient was most uncomfortable. There were no audible fetal heart sounds although the patient felt fetal movements. Rectal examination disclosed no presenting part.

When she was about eight months' pregnant, her membranes ruptured suddenly at home and she discharged a large amount of amniotic fluid. In the interval between the time she called her physician and his arrival she weighed herself and

granulosa cell tumors. The patient seems to be the youngest yet to be reported to have had this disease. When this report was written, three years and two months subsequent to operation, the girl was apparently well. The case is one of that small group (5 to 10 per cent) of cases in which the condition occurs before puberty. It is further unique in that the tumors were bilateral; bilaterality occurs in not more than 5 per cent of all cases of granulosa cell tumor.

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CASE OF DIPROSOPUS TETRANOPHTHALMOS

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DIPROSOPUS is a term applied to a fetal monster having two faces but with close union of the heads and bodies throughout. It is a rare teratism in man, being considerably more common in lower animals, especially the cow and cat. The duplication is not limited to the head but, as clearly shown in radiographic studies, includes the trunk as well. The double spinal column at times is well marked as far down as the sacrum, according to Dorland and Hubney's¹ *The X-ray in Embryology and Obstetrics*. Unlike most of the cases reported, which are of the triophthalmic type, my case is one of tetranophtthalmia. It is of interest not only because of its rarity, but because roentgenographic studies of the monster in utero were obtained, thus leading to a prepartum diagnosis of monster and preparing the family to expect a malformed, nonviable child.

The etiology of the condition is not known. It is either a splitting of a primitive stick or the fusion of two primarily developed ones, the former being the more tenable theory. This report will not touch upon the classification of double monsters, as any good textbook on obstetrics includes these interesting and rare studies.

In 1921, Beach² reported a case of derodidymus (dicephalus) with a review of some of the cases which had occurred prior to his report. His case was in a normal female, aged 29 years. After difficult manipulation lasting forty-five minutes, the patient was delivered of the monster. The specimen was of the dicephalic type with two vertebral columns joining the one sacrum.

Also in 1921, Cibelius³ reported a case of dicephalus with two complete spines. His case was a secundipara, aged 20 years. The delivery was difficult, a breech, with simultaneous delivery of the two heads. Study of the case revealed two hearts, two aortic arches, two superior vena cavae, two inferior vena cavae, and two thoracic aortas. The abdominal findings were indistinct.

Gaddie and Sims,⁴ in 1929, reported a case of anacatadidymus. Their case, a septipara, aged 35 years, was a spontaneous delivery, the monster weighing eleven pounds. One skull was of normal size and the other about two-thirds normal. Their report contains minute detail of roentgenographic and necropsy examinations of the interesting specimen.

well formed. The same is true for the bones of the pelvis and each lower extremity. There are twelve ribs on each side in perfect development in the anterior-posterior view, but in the lateral view, there is a marked kyphosis of the lower dorsals. This had distorted the position of the ribs posteriorly so that their attachments to the spine on each side are at acute angulation. The specimen, from the radiological standpoint, is considered to be an unusually rare one."

Postnatal Review of "In Utero" Films.—"In reviewing the films of the monster in utero, it is impossible to outline the double faces of the specimen. In the anterior-posterior view of the abdomen, the skull was superimposed upon the maternal pelvis. The lateral view demonstrated only the superimposition of the two faces. The kyphosis of the specimen was clearly demonstrable."

SUMMARY

1. An unusual and rare case of fetal monstrosity is reported.
2. I have been unable to find a similar one in the literature at my disposal.
3. An interesting comparison is shown between the pre- and postnatal roentgenologic studies of the case.

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RECESSION OF TOXEMIA FOLLOWING THE INTRAUTERINE DEATH OF ONE OF DIZYGOTIC TWINS

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WE HAVE been urged to report the following case because of its interest and any possible light it may throw on the etiology and pathologic physiology of eclampsia. We purposely refrain from drawing any implications or interpretations of our own.

Mrs. I. A., a Jewish primipara, aged 34 years, presented herself for prenatal care at the end of her seventh week of pregnancy. She had been married two months. Her last catamenia started July 7, 1939, making her estimated date of confinement, April 13, 1940.

Her past history was negative. She complained chiefly of an almost continual nausea and vomiting, in spite of which she had gained six pounds over her original weight of 125. Blood pressure was 110/70. Urine and Wassermann examinations were negative.

The patient was seen one month later, during which time she had a two weeks' illness with severe upper respiratory infection. Routine physical examinations revealed essentially negative findings. Head, throat, teeth, heart, lungs, abdomen, and extremities were normal. The uterus was 2.5 cm. above the pubis. Pelvimetry showed: intercrystal diameter 28 cm., interspinous 20 cm., external conjugate 20 cm., and transverse outlet 10 cm. The sacral promontory could not be felt.

Subsequent monthly office visits showed no abnormalities until the twenty-eighth week, Jan. 18, 1940, when it was noted that the blood pressure was 140/90 and weight 151 pounds. Edema of the feet and ankles and albuminuria did not appear until the thirty-third week.

Expectant treatment with rest, limitation of fluid intake, salt-free diet, and increased elimination was instituted. The patient was seen at weekly intervals, and the signs and symptoms of toxemia progressed. By March 10, the thirty-sixth week, the hands and face were markedly puffy, the urine was heavily loaded with albumin, and the blood pressure reached 150/100. Her weight was now 160 pounds.

found she weighed thirteen pounds less since the membranes had ruptured, an indication of the excessive amount of amniotic fluid. She was taken to the hospital at once.

The labor was comparatively long, 28½ hours. The delivery was spontaneous, a vertex presentation, which presented no particular difficulty under nambutal and scopolamine analgesia and gas oxygen anesthesia. The fetus was stillborn but not macerated. The puerperium was satisfactory and the patient was discharged from the hospital on her tenth post-partum day.

The fetus itself was a well-formed female, weighing exactly five pounds and was 19½ inches in length. It was essentially normal in appearance anteriorly except for the face (Fig. 1). Two complete faces were present with fusion of the ears in the center. Posteriorly there was a wide area, some four inches across,



Fig. 1.



Fig. 2.

of the bifid spine which extends from the lower thoracic area to the occiput where it broadened into a bloody mass in the occiput itself composed of brain tissue covered by the meninges. Necropsy was not performed because I wished to preserve the specimen intact for museum purposes. The x-ray study of the fetus follows (Fig. 2):

Roentgenologist's Report on the Specimen.—"The x-ray examination of the monster discloses a diprosopus tetranophthalmos. The diprosopus specimen demonstrates two well-developed lower mandibles with the dental buds in each lower mandible well arranged. The lower right side of one frontal is fused with the left side of the opposite fetal frontal. Four orbits are well formed. There are two separate sets of cervical vertebrae extending up into the individual skull bases. There is fusion of the spine at the first dorsal. Below this, there are two separate spines until the fifth lumbar is reached, where there is fusion and an accessory vertebra on the right side. Both clavicles, scapulas, and the bones of each arm are

UNILATERAL TWIN ECTOPIC PREGNANCY

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BETWEEN 1891, when De Ott¹ reported the first authentic case of unilateral twin ectopic pregnancy and August, 1939, when Kaplan² published two more case reports, a total of 67 instances have been presented in the world's literature. The interval papers of Arey³ in 1923 and Falk and Blinick⁴ in 1938 have been extremely effective in reviewing the recorded cases, bringing the totals to 40 and then 65. One other study has since been presented since Kaplan's paper, Recek reporting a case in May, 1939.⁵ The following study is the only case that has occurred in the five-year existence of the Queens General Hospital, during which time there have been 4,222 gynecologic admissions, 7,530 obstetric deliveries, and 54 ectopic gestations, all the latter proved at operation.

Mrs. H. B. (No. A836) was admitted to the Second Gynecological and Obstetrical Service of the Queens General Hospital on Sept. 30, 1939, complaining of eight hours of severe abdominal pain. The patient was a 25-year-old white housewife, whose medical and surgical past were entirely negative. Two previous pregnancies terminated in 1930 and 1932 in normal spontaneous deliveries at term. In 1935, the patient had a spontaneous abortion. None of these pregnancies were followed by a febrile course or any abdominal complication. Her last menstrual period began on July 15, 1939, and was normal in every respect.

Ten days before admission, on September 20, vaginal spotting was noted for the first time, lasting one day and subsiding spontaneously. Again on September 25 this slight spotting was seen by the patient, this time associated with lower abdominal cramps lasting two days and then disappearing spontaneously. During neither of these two episodes did the patient seek medical attention. On the day of admission there was a sudden recurrence of the pain, similar in character, localized to the right lower abdominal quadrant, far more severe than previously noted, associated with an initial attack of emesis and followed by intense perspiration and chills. In the eight-hour interval before admission to the hospital, there was no episode of fainting or shoulder pain.

When admitted to the hospital, the patient was acutely distressed. The blood pressure was 110 mm. of mercury systolic and 76 diastolic, pulse 100 per minute, and the temperature 99.4° F. The lungs and heart presented no pathologic findings. The abdomen was distended, diffusely tender, and showed marked rebound tenderness in both lower quadrants. The lower abdominal areas were spastic to deep palpation; no masses could be outlined. On vaginal examination it was found that the cervix was in the axis of the vagina, soft, and extremely tender on motion. The uterine fundus was anterior and, although not clearly defined, gave the impression of being slightly enlarged. In the left fornix, a soft, tender mass about 4 or 5 cm. in diameter was palpated. No bulging could be found in the posterior cul-de-sac. The urine was normal. Blood examination revealed a white cell count of 11,800 with 84 per cent polymorphonuclear cells, a red cell count of 3.5 million cells, and a hemoglobin of 11 Gm. (Sahli). The Kline test was negative.

Diagnosis was ruptured ectopic pregnancy, and the patient was immediately prepared for operation. Under cyclopropane anesthesia, the abdominal cavity was opened with the release of large amounts of clotted and fluid blood. The uterus was softened and enlarged to the size of a two months' pregnancy. Both ovaries and the right tube were normal. The left tube was dilated at the junction of the middle and outer thirds, the dilatation presenting a distinct area of rupture with a slow, constant ooze of blood. A left salpingectomy was performed, including the excision of the cornual end of the tube. The patient's postoperative course was uneventful, and she was discharged on her eleventh convalescent day in excellent condition.

Ten days later, to our amazement, the albuminuria and edema had disappeared. The blood pressure was still elevated. The cervix was effaced, thin, and 2.5 cm. dilated. The baby was active, and the fetal heart was distinctly audible in the left lower quadrant. We were at a loss to explain this sudden clinical improvement.

When seen a week subsequently, March 27, the blood pressure was 144/90, and she was free of albumin and edema. Her weight was 152 pounds.

Labor began spontaneously, April 1, 1940, two weeks before the estimated date of term. She was admitted to the Massachusetts Women's Hospital and after four and one-fourth hours of labor she was delivered normally of a female child, L.O.A. position, weighing 5 pounds 8 ounces. The baby was normal in every way. Six minutes later a second fetus, male, macerated, stillborn, R.S.A. position, weighing 3 pounds 5 ounces, was extracted. The extent of maceration was deemed to coincide with the duration of clinical recession of the toxemia. The placentas were expressed five minutes later. They were fused and platter shaped.

The mother and live baby progressed uneventfully and were discharged from the hospital on the seventeenth day post partum.

PATHOLOGIC REPORT (DR. J. STEWART ROONEY)

Gross Examination.—Specimen of double ovum, fused, twin placentas weighing 630 Gm. and measuring 19 cm. across the septum. One placenta measured 12 cm. in diameter, while the other measured 17 cm. One cord was marginally attached, measuring 40 by 1 cm., while the other cord was attached 3 cm. from the margin and measured 40 by 1 cm. There was no anastomosis of the vessels. The membranes (the septum) consisted, in succession, of amnion, chorion, chorion, and amnion. The fetal surface was slightly meconium stained and suggested maceration. The maternal surface was pale. A cut across the septum showed a marginal area of yellow, granular, ischemic necrosis on the smaller side which looked diffusely avascular compared to the larger side.

Microscopic Examination.—Sections through the avascular placenta showed a marginal area of ischemic necrosis, with necrosis of the underlying decidua. Elsewhere the decidua showed the characteristic moth-eaten and fibrinoid degeneration. The chorionic villi were slightly immature in size and shape and showed slight necrosis of the stroma. The surface syncytium showed fewer knots than in maturity. The larger vessels of the main-stem villi and chorionic plate contained moderate numbers of red cells, but the villi were otherwise avascular, and there was almost no blood in the intervillous spaces. A second section through the septum between the two placentas showed the avascular placenta as described above. The vascular placenta showed slight immaturity of the chorionic villi, but the vessels were filled with red cells and there were moderate numbers of red cells in the intervillous spaces. The membranes showed the gross findings of two chorionic membranes each with its amniotic membrane showing slight maceration.

Diagnosis.—Double ovum twin placentas, fused, one battledore with ischemic necrosis (white), avascular, with maceration and meconium staining; one slight premature placenta; placenta from twins; one macerated stillborn, and one living infant.

SUMMARY

A primipara, aged 34 years, with a twin pregnancy, developed signs of toxemia in the twenty-eighth week. The toxemia suddenly abated at the end of the thirty-sixth week. Two weeks before term she was delivered of dizygotic twins, the first a living female, and the second a macerated male. The latter's intra-uterine death was estimated as coinciding with the clinical recession of the toxemia. The placentas were fused and the cords were inserted marginally at opposite ends. The smaller placenta showed areas of ischemic necrosis.

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The pathologist's report of the tubal pregnancy was as follows:

"Gross.—The specimen (Fig. 1) consists of a cystic tubular mass measuring 8 by 3 cm. The external surface is smooth with a surface dullness. On cut section, the cystic content is found to consist of a clear fluid. A single large sac measures 6 cm. in length and $2\frac{1}{2}$ cm. in width. The inner amniotic lining is glistening and shows dilated, thin-walled superficial vessels radiating toward the umbilical cord which is well formed in one fetus. This well-formed fetus measures 2 cm. in length and has an attached yolk sac measuring $\frac{1}{2}$ cm. in diameter that is easily recognizable. The umbilical cord is short and shows some coils. The limb buds are easily distinguished. The other fetus is somewhat smaller in size and the presenting length measures only $1\frac{1}{2}$ cm. The limbs are not as differentiated. The wall of the mass shows thickening, hemorrhage and suggests an encircling chorion.

"Microscopic.—The section of the tube (Fig. 2) shows the hypertrophic muscular layer and the hyperplastic mucosa. In addition, the mucosa shows a decidua reaction with a large attached blood clot in which numerous chorionic villi are present.

"Diagnosis.—Twin tubal pregnancy, monochorial."

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28 STUYVESANT AVENUE

50 RIVERSIDE DRIVE

DIPHTHERITIC VAGINITIS IN THE ADULT

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THE Klebs-Loeffler bacillus grows best on an alkaline medium and in an abundance of air. It is rarely found in the vaginal flora. Since most women have some degree of immunity to diphtheria, it is quite uncommon for true diphtheritic vaginitis to occur in the adult.

In the following case, the predominating vaginal infection was a primary diphtheria with spontaneous expulsion of a complete cast of the vagina followed by vaginal atresia.

CASE REPORT

J. H., aged 22 years, colored, gravida iii, was admitted to Gallinger Municipal Hospital on Oct. 19, 1939, complaining of a painful sore on her perineum. She had had a slightly sore throat, fever, and a headache for a week. On Oct. 15, 1939, the patient became aware of a nodular swelling of the right labium majus and of an ulcer of the perineum with associated severe and persistent pain. The patient's mother had been treating the ulcer with a cresol antiseptic solution. Menstrual periods had been regular. Last period began on Oct. 11, 1939, and was completed the day before admission. Patient had given birth to two full-term infants. Last pregnancy terminated spontaneously in the fifth week in 1935. She had been married twice. Past medical history included whooping cough, measles, and mumps. In 1936, the patient was treated for gonorrhea.

Physical Examination.—Patient was a well-developed, fairly well-nourished, acutely ill, colored woman, restless and in severe pain. Temperature, 103.2° F.; pulse, 122; respirations, 24; and blood pressure, 110/52. Skin was hot and dry. Gums receded. Tongue was coated. Pharynx showed slightly reddened areas around the faucial ring, but no ulceration or membrane. Chest, breasts, and heart were normal. Abdomen was flat and soft with generalized tenderness to palpation. External genitals were edematous. A tender, fairly firm, right Bartholin gland, 6 cm. in diameter, was present. A ragged, granular, reddened ulcer, 3 cm. by 4 cm. in-



Fig. 1.—Dilated portion of tube divided to show the single chorionic sac surrounding the two fetuses.



Fig. 2.—Section of the wall of dilated tube showing flattened epithelial folds, chorionic villi, and blood clot.

Society Transactions

CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
TWELFTH ANNUAL MEETING, INDIANAPOLIS, IND.,
OCTOBER 10 TO 12, 1940

The following papers were presented:

Presidential Address: Continuation Study. Dr. Jennings C. Litzenberg, Minneapolis, Minn. (For original article, see page 547.)

Local Anesthesia in the Second and Third Stages of Labor. Dr. Roy E. Crowder, Sioux City, Ia.

The Relative Effect of Analgesia and Anesthesia in the Production of Asphyxia Neonatorum. Drs. Harold Henderson, E. Bruce Foster, and L. S. Eno, Detroit, Mich. (For original article, see page 596.)

Solid Teratoma of the Ovary in the Young Girl. Dr. Merrill Smeltzer, Detroit, Mich. (For original article, see page 616.)

Dental Caries in Pregnancy. Dr. Joseph D. James, Springfield, Mo.

A Study of One Hundred and Seven Cases of Uterine Bleeding With Endometrial Biopsies. Dr. Gilbert F. Douglas, Birmingham, Ala. (For original article, see page 624.)

The Leucocyte Count in Labor. Dr. John R. Wolff (by invitation), Chicago, Ill. (For original article, see page 611.)

The Differential Diagnosis of Acute Appendicitis in the Female. Dr. H. E. Schmitz, Chicago, Ill.

The Vaginal Smear (Papanicolaou) Prior to the Menopause in Menstrual and Reproductive Disorders. Dr. P. F. Schneider, Evanston, Ill.

The Economic Status of Obstetrical Care in North Dakota. Dr. P. W. Freise, Bismarck, N. D.

Inhibition of Lactation. Drs. H. L. Stewart, Jr. (by invitation) and J. P. Pratt, Detroit, Mich. (For original article, see page 555.)

Some Aspects of the Pathology of Hydatidiform Mole and Chorionepithelioma. Dr. Robert Meyer, Minneapolis, Minn.

Blood Prothrombin Levels in the Newborn. Drs. Carl P. Huber and Jack C. Shrader (by invitation), Indianapolis, Ind. (For original article, see page 566.)

Breech Delivery. Dr. Elmer M. Hansen, Lincoln, Neb. (For original article, see page 575.)

The Therapeutic Value of Tubal Patency Tests in Sterility and Infertility. Drs. M. L. Leventhal and E. M. Solomon (by invitation), Chicago, Ill. (For original article, see page 628.)

Conglutinatio Orificii Externi as a Factor in Delayed Labor. Dr. Philips J. Carter, New Orleans, La. (For original article, see page 606.)

Pituitary Extract for Dystocia Due to Uterine Inertia in the First Stage of Labor. Drs. R. S. Siddall and D. G. Harrel (by invitation), Detroit, Mich. (For original article, see page 589.)

Are the Anterior Pituitary-Like Substances Gonadotropic? Drs. Willis E. Brown, Omaha, Neb., James T. Bradbury, Ann Arbor, Mich., and Ida Metzger, Ypsilanti, Mich. (For original article, see page 582.)

volved the fourchette. Foul, yellowish brown, watery discharge was coming from the vagina. As much of the vaginal mucosa as could be exposed appeared gangrenous.

Laboratory Findings.—Repeated smears and culture were negative for gonococci. Dark-field examination was misleading in that spirochetal organisms were found, but they were not identified as the *Treponema pallidum*. Kahn tests were negative on Oct. 19, 1939, Nov. 27, 1939, and Jan. 24, 1940. Urinalyses were normal except for one-plus albumin. Blood count varied from Hb. 70 per cent; red blood count 3,000,000, white blood count 14,700, on admission to a low of Hb. 33.4 per cent, red count 2,600,000, and white count 7,000, on Nov. 24, 1939.

Progress.—Preliminary diagnoses were confusing. Acute Bartholinitis was obvious, but gonococci were absent in smears and culture. The ulcerative lesion suggested secondary syphilis, but the Kahn test was negative. Etiology of the gangrenous vaginitis remained obscure until Oct. 26, 1939, when the patient passed a hollow cast of the vagina 10 cm. by 7½ cm. by 1 cm. External surface of the cast was dirty, grayish brown, and moderately trabeculated throughout. Inner surface was granular, covered by a light brown cheesy material. Cut surface showed a homogenous gray tissue. Microscopic examination of the cast showed a mass of necrotic tissue. McCallum stain showed the presence of diphtheria bacilli in the necrotic tissue. Following passage of the cast, the vagina showed rough, granular, extremely tender areas of ulceration.

The cast suggested diphtheritic vaginitis. Vaginal and nose and throat cultures were taken immediately. Three nose and throat cultures were negative for diphtheria. Two vaginal cultures were morphologically positive for diphtheria. Virulence tests were positive. On Nov. 3, 1939, the patient's five-year-old daughter was admitted to the Isolation Ward with faucial diphtheria. The child had had a sore throat for four days.

Before discovery of diphtheria, the patient had been given sulfanilamide and a blood transfusion. Fever was irregular ranging from 98 to 104° F. Following the injection of 20,000 units of diphtheria antitoxin and a second blood transfusion, clinical improvement was rapid. By Nov. 17, 1939, the ulcer of the fourchette had healed completely, the right Bartholin gland was soft, fluctuant, and non-sensitive. Fibrinous adhesions between the cervix and vagina obliterated the vaginal vault. Under evipal anesthesia, the thin vaginal adhesions were dissected digitally and the vagina was packed tightly with vaseline gauze. Packing was removed on the fifth postoperative day. At the time of discharge from the hospital, Dec. 7, 1939, three negative vaginal cultures for diphtheria had been obtained. The vagina was showing some generalized constriction. One week later, there was an annular constriction just inside the hymenal ring which reduced the orifice to a diameter of about 2 cm. Dense adhesions had formed around the cervix.

During the year that the patient has been under observation, constricting bands have been excised from the vagina twice. The right Bartholin gland has been removed. Culture of its contents was negative for diphtheria. For the first five months after leaving the hospital, the patient wore a pyrex vaginal plug constantly. Severe postinflammatory scarring of the vault has reduced the depth of the vagina to about 5 cm. However, the vaginal orifice admits three fingers. The cervical os has remained open. The patient has had no dyspareunia, and menstrual function has remained normal.

This case demonstrates the value of accurate laboratory data in the differential diagnosis of ulcerative vulvovaginal lesions, confirms the importance of specific therapy in genital diphtheria, and presents a problem in acquired vaginal atresia.

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Correspondence

Relation of the Pituitary to the Etiology of Eclampsia

To the Editor.—

Dr. Geiling's collective review of the pharmacology of the pituitary in the November, 1940, issue of this JOURNAL admirably epitomizes present knowledge. There are, however, certain statements concerning "hypersecretion of the posterior lobe of the pituitary" related to the cause of eclampsia, which call for qualification and elaboration.

Basing my arguments on clinical observations and biologic experiments, I postulated the heightened activity of postpituitary principles in the pregnant organism sensitized by split-products of proteins, as derivatives of disintegrated syncytial elements, as a basic factor in the pathogenesis of pre-eclampsia and eclampsia. (Zentralbl. f. Gynäk., January, 1918.) As a corollary, I suggested the administration of corpus luteum preparations as a suitable method of therapeutically counteracting the hyperactive pituitary hormones (Zentralbl. f. Gynäk., 1920). To the usefulness of such treatment, proper emphasis was given on the basis of more extended investigations in later years, by Corner, Robson, McIlroy (Edinb. M. J., 1937; Tr. ed. Ob. Soc., p. 61), while Robson and Paterson, Young suggested that progesterone deficiency may be actively concerned in the pathogenesis of eclampsia (Brit. M. J. 1: 1937).

The effects on vital organs of overdosage of pituitary pressor principles, as giving some indication of a hyperfunction of the gland itself, were studied with unflinching interest and energy. Designed to test our concept, Knepper obtained evidence of the occurrence in dogs, as the result of parenteral injections of proteins and subsequent exhibition of pitressin, of lesions in the parenchyma of the liver, the lung, brain, and kidneys, closely resembling changes known to occur in eclamptics (Zentralbl. f. Gynäk., 1934). Dodds and Noble demonstrated the production of gastric and intestinal ulcers in rabbits (Nature 135: 788, 1935). Again, Byrom gave a critical digest of the experimental literature and demonstrated in the kidneys of rats which had received injections of vasopressin, lesions which were highly suggestive of those found in late toxemia of pregnancy. Of considerable interest were his additional studies showing that both, gonadotropic hormones and estrin, sensitize the blood vessels to vasopressin (Lancet 1: 129, 1939).

In support of my assertion, I subsequently endeavored to adduce telling arguments by pointing to a remarkable parallel between well-known characteristics of the blood chemistry in eclamptics and the findings in the blood of animals which had received intravenous administrations of posterior pituitary extract, notably the phenomenon of anoxemia of the tissues (AM. J. OBST. & GYN. 26: 311, 1933). There was also stressed the marked response of the arterioles of the kidney to pitressin (Richards) by way of constriction.

Efforts to obtain direct evidence for the integral endocrine factor, by establishing an excess of pitressin in the blood of pre-eclamptics, invited acrimonious debate, with denials of such findings far in preponderance (Theobald, Byrom and Wilson, Wesselow and Griffith, Hurwitz and Bullock). In like manner, the histologic basis of functional postpituitary hyperactivity conditioned by stimulation through the invasion of basophilic elements (H. Cushing) was unable to withstand criticism. Quite recently, however, the subject entered a new phase. The concept that *natural secretion* of pitressin may reach toxic levels and may induce intense vascular spasm, in consequence of a specific sensitization of the arteriolar tree and the abeyance of antipressor principles, becomes proportionately more acceptable. As to the former, the augmented thyroid activity during pregnancy with increased quantities in the blood of thyroxine and iodine (G. Curtis) deserves to be placed

NEW YORK OBSTETRICAL SOCIETY

MEETING OF NOVEMBER 12, 1940

The following case reports and papers were presented:

Report of a Case of Submucous Fibroid or Sarcoma Removed Vaginally During Labor. Dr. Richard N. Pierson.

Report of a Case of Lateral Pyocolpos With Absence of One Kidney. Dr. Max D. Mayer, and S. H. Geist.

Postpartum Sterilization. Dr. Fred L. Adair. (By invitation.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF NOVEMBER 15, 1940

The following papers were presented:

The Place of Surgery in Fibroids of the Uterus. Dr. C. W. Barrett.

The Occurrence of Diphtheria Antitoxin in the Human Pregnant Mother, New-born Infant and the Placenta. Drs. J. Liebling, G. P. Youmans and H. E. Schmitz. (For original article, see page 641.)

Pituitrin Shock. Drs. M. H. Adelman and B. B. Lennon. (For original article, see page 652.)

Lissimore and Currie: Studies in Vaginal Fluid, J. Obst. & Gynaec. Brit. Emp. 46: 673, 1939.

A series of 105 cases of vaginal discharge was examined. The majority of patients (66.9 per cent) were the hosts of *Trichomonas vaginalis*. This organism in the opinion of the authors is not pyogenic but is associated with a lowering of the normally high acidity of the vaginal contents, and thus with removal of one of the most powerful barriers to infection by pyogenic invaders, of which the *Staphylococcus pyogenes aureus* is by far the commonest in their series. This accounts for the frequent association of the flagellate with pus, secondary infection being more usually present. There are two possible explanations of this association of the flagellate with decreased activity:

A. The trichomonas is antagonistic to the bacillus of Döderlein. It also impedes the normal desquamation of vaginal epithelium. Thus both factors, closely associated with normal vaginal acidity, are reduced or absent.

B. The acidity of the vagina suffers great antecedent reduction by at least two natural factors, namely (1) the presence of menstrual lochia during periods, and (2) the deposition of semen during intercourse. The trichomonas, finding once again a medium of a pH agreeable to its existence, readily reestablishes itself. It is thus not necessary to postulate direct infection from the male during intercourse. Either of these two factors would explain the reappearance of trichomonas after apparent cure.

In the 33.1 per cent of cases in which trichomonas is absent, pyogenic infection explains the qualitative abnormalities of the vaginal fluid, and, as in the trichomonas positive cases, the *Staphylococcus pyogenes aureus* appears to be the commonest invader.

J. P. GREENHILL.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Malignant New Growths

Reidiger, K.: A Plan of Cancer Control in East Prussia, *Deutsche med. Wchnschr.* 66: 155, 1940.

The author discusses the difficulties of discovering carcinoma in the examination of large groups of women. In 1,920 women examined, carcinoma of the breast was found in 7 cases, suspicious growths in 11. Carcinoma of the uterus was diagnosed in 4 cases, suspected in 36 others. Associated genital pathology was found in 645 cases. The technique of polariscopic examination of the blood serum for cancer, as developed by Brdička and Waldschmidt-Leitz, is fully described. Waldschmidt-Leitz claims to have a histologically proved accuracy of 95 per cent in over 500 cases of cancer diagnosed by this method. Reidiger favors the routine use of the colposcope.

R. J. WEISSMAN.

Filkel: Polarigraphic Study of Serum of Women With Carcinoma of the Genitalia, *Zentralbl. f. Gynäk.* 63: 647, 1939.

A new serologic test for carcinoma is described by Filkel. In 176 cases of carcinoma, diagnosis was correctly made in 92.6 per cent, and among 107 cases of recurrence of cancer, the incidence of correct diagnosis was 88.9 per cent. Early carcinoma could be detected in 87 per cent of the cases. However, the cancer reaction is not specific, because a positive test may be obtained in cases of pelvic inflammation. Despite this, the test proved helpful in cases of recurrence and in doubtful cases.

J. P. GREENHILL.

Morse, A. H.: Problems and Errors in the Diagnosis of Cancer of the Uterus, *Connecticut State M. J.* 4: 461, 1940.

One would assume that the recurrence of bleeding, subsequent to a complete freedom from discharge over an interval of months or years, would prove of significance to the patient or to her relatives, but too frequently the symptom is disregarded.

If ever we are to see the early stages of cervical malignancy, we must cease relying upon what are designated as the first signs of cancer, but must emphasize the necessity of a routine yearly, or better semi-annual, examination of the pelvic organs, even though no symptoms are present, for women in the menopause.

From a survey of a group of histories, however, it is clear that there are some members of the profession who wholly disregard the possible significance of abnormal uterine bleeding or who fail to suspect malignancy even when it is present. In 10 patients whose histories were reviewed, vaginal bleeding, in some instances profuse, was the sole cause of the visit to the physician. However, it appears that no pelvic examination was made in any of these cases. Some women were given a drug by mouth or vaginal douches were prescribed. Others were told that the bleeding was of no significance.

If the general practitioner can be brought to realize that the presence of abnormal discharge or bleeding from the vagina makes a pelvic examination imperative, it will be a great step forward.

J. P. GREENHILL.

first on record (Clark). Certain split products of proteins, particularly histamine-like substances (Paulsson, Carleton), the above-mentioned sex hormones, hyperplasia of the adrenal cortex and the concomitant alteration of the salt balance, represent significant factors which may conduce to a heightened responsiveness of the arterioles to vasopressin. In normal pregnancy, an inhibitory factor which holds the effect of such stimuli in check was to be searched for. The key to the acute problem seems to be provided by consideration of the remarkable quantities of acetylcholine stored in the normal placenta.

Information bearing on a substance significantly constant, both as to presence and quantity in normal human placentas and pharmacologically identified as acetylcholine, had its inception in the investigations of Bischoff, Strack and Loeschke, Hauptstein, Chang and Gaddum (J. Physiol. 79: 274, 1933). The release of acetylcholine into the maternal circulation is contingent on the unique position of the human placenta to maintain a broad and direct contact with the maternal intervillous blood spaces and continuously to shed from its surface syncytial buds with hormones and other chemical entities, stored or elaborated within the placenta. The recent experimental demonstration of an antagonistic pharmacodynamic action on the arteriolar tree of pitressin and the powerful vasodilator acetylcholine (Necheles and Neuwelt, Am. J. Physiol. 124: 142, 1939) is of immediate interest and gives weight to the concept of the existence during normal gestation of a specific biochemical blood pressure regulating mechanism concerned with maintaining a well-defined equilibrium between pressure-raising principles and acetylcholine.

The assertion that pre-eclampsia virtually illustrates a dislocation of this equilibrium, with the arterioles hyperreactive to pitressin, will be found to diverge from obstetric orthodoxy which steadfastly clung to the idea that the placenta is the source of certain toxins. Presentation of the following facts, however, serves to bear out our contention. Determination of the acetylcholine content of placentas obtained from severe pre-eclampsics revealed quantitative data distinctly below the almost constant normal levels of 90 to 120 mg., calculated in terms per one kilogram of fresh organ. A preliminary report of this work was presented, in discussion, at the last meeting of the American Medical Association and an attempt made to correlate such *placental deficiency* with the well-known occurrence in the toxemic placenta, of multiple areas of infarction and autolysis. Spaeth, Eufinger and Sprado, of late, investigated the values for blood choline in normal and toxemic women and reported a marked decrease in 9 cases of pre-eclampsia studied. Eight out of 9 cases of eclampsia gave unusually low figures (Monatschr. f. Geburtsh. u. Gynäk. 101 and 102: 1935, 1936).

Quite recently, through the kind cooperation of the department of pharmacology of Harvard Medical School, evidence was obtained concerning a most remarkable increase in placental tissue of the concentration of choline-esterase, in severe pre-eclampsia and eclampsia. Since the physiologic function of the enzyme concerns the removal of the acetylcholine liberated, strong support is obtained in favor of our conception.

The presumed function during gestation of placental acetylcholine as opposing the action of pitressin well accords with recent discoveries in animals of an inhibitor substance present in extracts of kidney and muscle. Significantly, decreased concentration of this substance renders animals unusually sensitive to the effects of renin (Page, Grollman, Tillman). The significance of reduced renal blood flow in the late toxemia of pregnancy, as the result of pitressin-induced angiospasm, is unequivocally portrayed in the experimental studies of Goldblatt.

J. Hofbauer, M.D.

Cincinnati, Ohio
Jan. 31, 1941.

Hall, Norman D.: *Carcinoma of the Cervix in the First Three Decades of Life*, Canad. M. A. J. 43: 362, 1940.

Of 134 cases of uterine carcinoma occurring in persons under 30 years of age 57 represented carcinoma of the cervix. This is 7.4 per cent of all proved cervical carcinomas seen at the institution. There has been a proportionate increase in the frequency of cervical carcinoma in women 30 years of age or under during the past five years as compared with the previous five years. At least 37 per cent of this group were married before the age of 20 and 37 per cent had had one or more pregnancies before 20 years of age. The youngest patient seen was 20 years old. Abnormal bleeding was the first symptom in 95 per cent of the patient and was the only symptom in 50 per cent of the group. Of this group, 49 per cent died within two years after the diagnosis was made, and only 11.5 per cent lived over two years.

CARL P. HUBER.

Diddle, A. W.: *Carcinoma of the Cervix Before the Age of Twenty Years*, Am. J. Cancer 34: 207, 1940.

From July, 1926, to Dec. 1, 1939, 505 cases of carcinoma of the cervix were diagnosed in the University Hospitals (Iowa). Five of the patients were less than 25 years of age; one was 17 years, two 21, one 23, and one 24. The available literature reveals 18 reports of cervical malignancy occurring before the age of 20. Only three of the tumors were designated as epitheliomas, while 9 were adenocarcinomas, and in six the type is not indicated. Of the 18 patients, 6 died within one year.

The impression is obtained that the prognosis of carcinoma of the cervix before the age of 20 is grave because of the accelerated growth impulse in malignant neoplasms during the growing years. The case reported by the author demonstrates the rapidity with which the neoplasm may invade the surrounding pelvic tissues, even during heavy irradiation therapy.

J. P. GREENHILL.

White, J. W.: *Carcinoma of Uterine Cervix*, Am. J. Surg. 45: 4, 1939.

Microscopic examination of adequate biopsy material is the only means by which cancer of the cervix can be diagnosed with any degree of precision, and little hazard is involved in properly excising biopsy specimens. Colposcopic examination and the Schiller iodine test are of academic interest. Both are greatly subsidiary to unaided visualization and biopsy. The Schiller test is a purely negative diagnostic method. Palpation of the cervical broad ligaments is satisfactorily accomplished by a combined vaginorectal examination. The majority of cervical cancers are radiosensitive; and the more active and anaplastic the cells, the less their radio-resistance. Cancer appearing in the cervical stump within one year after supravaginal hysterectomy is residual and was present before the operation. If it appears after a longer interval, it must be considered a subsequent primary new growth. As prophylaxis against the latter event the mucosa of the cervical stump including the endocervix, if not destroyed by cautery at the time of operation, must be so destroyed within four weeks thereafter. Radium irradiation efficiently administered is the safest and most certainly curative method of treatment, but it must be supplemented by high voltage roentgen rays in all except the earliest cases. Primary roentgen therapy, supplemented by postradium roentgen irradiation, offers advantages that require further evaluation. Radium is by no means a simple remedy that may be applied casually without disastrous effect or serious consequences. Therefore, it should be used only by those who have had an opportunity through supervised experience to become expert in its application. Although the absolute curability rate for cancer of the cervix is between 20 and 30 per cent, half the total number of patients treated will die of the disease within three years.

J. P. GREENHILL.

Peller, Sigismund: *Cancer and Its Relations to Pregnancy, to Delivery, and to Marital and Social Status*, Surg., Gynec., & Obst. 71: 1, 1940.

The distribution of primary neoplasms within the breast and genital organs, and the age-specific death rates from cancer of each part are widely influenced by birth rates; the total mortality from cancer of the breast and genital organs, however, varies only to a small degree, as an increase in incidence in one organ is compensated for by a decrease in incidence in other organs. The compensation is not an exact one, for populations with higher birth rates have a rather diminished mortality. These findings are corroborated by the clinical studies of the author (1922 to 1923).

From the standpoint of social status the changes in the incidence of uterine cancer and breast cancer become apparent. These changes are independent of those due to purely biologic relations, that is fertility and cancer rate.

In contradistinction to the factors considered, circumstances attendant upon the husband's death are likely to increase the mortality from both uterine and breast cancer, and so to change the age-specific frequency of cancer affecting both organs.

The lower the social level and the less satisfactory the marital status, the earlier the patient manifests cancer or dies from it.

The correlation between cancer and pregnancies in women is entirely different from that in mice.

WILLIAM C. HENSKE.

Peller, Sigismund: *Cancer and Its Relations to Pregnancy and Delivery to Marital and Social Status*, Surg., Gynec., & Obst. 71: 181, 1940.

The total cancer mortality as well as the site of the primary tumor (genital organs, breast, stomach, biliary system, pancreas, and colon) is influenced by the marital status. During the age of reproduction married women show higher cancer rates than do spinsters; in the twenty years following, there are small differences in favor of married women; above the age of 64 both groups have about equal cancer mortality rates. These cases differ from one another only in the distribution of the primary tumors. In widows the age specific mortality rates are higher for cancer of genital organs, breast, stomach, pancreas, and colon than in single or married women; widows also succumb more frequently to gall bladder cancer than do single women.

There is a correlation between reproductive activity and the changes in the cancer distribution within the genital organs, the breast, biliary system, and stomach, the incidence increasing in some organs and in others diminishing. These changes counterbalance each other.

The simultaneous occurrence of cancer with pregnancy seems less frequent than would be expected, the deficit increasing as age advances, and as the average number of pregnancies increases.

WILLIAM C. HENSKE.

Leissner, H.: *Myoma and Carcinoma of the Body of the Uterus*, Acta. obst. & gynec. Scand. 20: 106, 1940.

The author noticed a high frequency of the association of myomas with carcinoma of the uterine body, and reviewing the literature found this to be a fairly common observation. He points out that there is a far greater association of corpus carcinoma with myoma than of cervix carcinoma with myoma. He believes that myomas may play a part in the development of cancer of the endometrium, and that hyperplasia of the endometrium is an intermediary stage in the development of cancer. He found that corpus cancer usually is located in places which are difficult to reach, such as the site of attachment of the myoma to the uterus and in hidden corners.

J. P. GREENHILL.

Warren, Shields, Meigs, Joe V., Severance, Alvin O., and Jaffe, Henry L.: *The Significance of the Radiation Reaction in Carcinoma of the Cervix Uteri*, Surg., Gynec., & Obst. 69: 645, 1939.

The histologic grade of carcinoma of the cervix is of less importance in prognosis than the clinical classification.

The response to radiation of either tumor cells or stroma is a definite guide to radioresistant cases; practically all those failing to show radiation changes on the early biopsies die of their carcinoma in spite of intensive radiation therapy. It is believed that such cases should be treated surgically.

WILLIAM C. HENSKE.

Meigs, Joe V., and Jaffe, Henry L.: *Carcinoma of the Cervix Treated by Roentgen-Ray and Radium*, Surg., Gynec. & Obst. 69: 257, 1939.

This paper deals with 70 patients who have been followed and studied very carefully. It shows that the results of the treatment of cancer of the cervix with x-ray and radium are eminently satisfactory. It is evident that certain charts of prognostic value can be made, and the curves induce the authors to believe that it is no longer necessary to follow patients for five years before reporting on them but that a three-year follow-up from the time of treatment should suffice. If, from the end-results at three years, 15 per cent is deducted for the next two years, the approximate five-year results can be predicted. Therefore, more opportunities are given to the gynecologist and radiologist to change a given form of treatment.

The routine study of microscopic slides, while the patient is being seen, is of great value. The presence or absence of a proper microscopic radiation reaction is an important prognostic sign. The authors advise that in every cancer clinic the slides be looked at at the same time that the patients are examined.

Biopsies should be taken before treatment starts and after treatment to determine whether or not radiation is satisfactory as determined by the radiation reaction.

In this series of cases it is evident that kidney lesions due to blocked ureters with subsequent uremia are among the chief causes of death. More urologic investigations should be undertaken and they should be made before, during, and following treatment. Any indication of ureteral block should be treated as early as possible.

Since using a slower type of treatment with x-ray and radium, the patients have been more comfortable and their convalescence, after leaving the hospital, has been much easier. This type of treatment delivers more effective radiation about and around the cervix than can be delivered by radium alone. Areas of tumor on either side of the cervix are certainly reduced in size and may be destroyed. The field of radiation in the broad ligaments and about the cervix before the radium is given is well walled-off by tissue reaction and fibrosis. Therefore, trauma of the cervix from curetting or application of radium will not cause extension of disease.

WILLIAM C. HENSKE.

Rosh, Rieva: *Factors Influencing the Prognosis in the Treatment of Carcinoma of the Cervix*, Radiology 35: 17, 1940.

The therapy and complications arising from the treatment of carcinoma of the cervix by means of roentgen rays are reviewed. This review covers a total of 795 cases observed in the radiation therapy department of the Bellevue Hospital. The author feels that there is no absolute knowledge by which one can determine which type of carcinoma is resistant or sensitive to radiation, and therefore no attempt was made to group this series according to histologic study. In general the course of the therapy consisted of preliminary x-ray therapy to the pelvis, followed by radium administration to the cervix and uterus, and subsequent x-ray therapy to the pelvis four weeks later. Certain well-known complications to the skin, urinary tract, pelvic lymph nodes, rectum, and vagina are discussed. The poor results in cervical

Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix,
League of Nations Health Organization 3: 1, 1939.

The definitions of the four stages of cancer of the cervix uteri accepted by the League of Nations are as follows:

Stage I. The carcinoma is strictly confined to the cervix.

Stage II. The carcinoma infiltrates the parametrium on one or both sides, but does not invade the pelvic wall. The carcinoma infiltrates the vagina, but does not involve its lower third. Endocervical carcinoma spreads to the corpus.

Stage III. The carcinomatous infiltration of the parametrium invades the pelvic wall on one or both sides. On rectal examination, no cancer-free space is found between the tumor and the pelvic wall. The carcinoma involves the lower third of the vagina. Isolated carcinomatous metastases are palpable on the pelvic wall (irrespective of the extent of the primary cervical growth).

Stage IV. The carcinoma involves the bladder as determined by cystoscopic examination or by the presence of a vesicovaginal fistula. The carcinoma involves the rectum. The carcinoma has spread outside the true pelvis (below the vaginal inlet, above the pelvic brim, distant metastases).

This annual report, the third of the series, includes statements from 16 radiotherapeutic centers.

The statements provided by these centers vary considerably with respect to the number of years to which they relate and to the number of patients treated yearly in each center. When all the data in them are combined, they furnish information concerning 9,061 patients suffering from cancer of the uterine cervix examined with a view to treatment, of whom 7,958 (87.8 per cent) were submitted to radiologic treatment.

The following tabular statement shows the results obtained after the lapse of five years from the date of treatment:

		PER CENT
Alive without recurrence	2,194	27.6
Alive with recurrence (including those operated upon after failure of radiotherapy)	128	1.6
Died of cancer	5,368	67.5
Died of intercurrent disease	163	2.0
Lost sight of	105	1.3
	<hr/> 7,958	<hr/> 100.0

The 7,958 patients treated were allocated to stages as follows:

		PER CENT
Stage I	871	10.9
Stage II	2,305	29.0
Stage III	3,420	43.0
Stage IV	1,360	17.1
Unclassified	2	0.03
	<hr/> 7,958	<hr/> 100.0

Results of treatment calculated for each of the four stages:

	NUMBER OF PATIENTS TREATED	ALIVE WITHOUT RECURRENCE	RELATIVE CURE RATE PER CENT
Stage I	871	498	57.2
Stage II	2,305	867	37.6
Stage III	3,420	754	22.0
Stage IV	1,360	75	5.5
Unclassified	2	0	0.0
	<hr/>	<hr/>	<hr/>
Grand total	7,958	2,194	27.6

The most striking feature of this study, aside from the pathologic findings, has been the realization that most patients come for treatment when they are already in an advanced stage and have had significant symptoms extending over from six to twelve months before seeking medical advice. With the remarkable progress that has been made in the techniques of therapy, the next step in the control of cervix cancer lies in the road of education, both lay and professional, to make both patients and physicians appreciate the possible significance of abnormal vaginal bleeding.

WILLIAM C. HENSKE.

Dörr, H.: Metastases in Genital Carcinoma of Women, Particularly Bone Metastases, Fortschr. a. d. Geb. d. Röntgenstrahlen 60: 100, 1939.

Dörr states that American radiologists maintain the rarest site for metastases of cervical carcinoma to be the bones of the skeletal system. Within the past year, however, he observed 10 cases of skeletal metastases. He had previously reported 2 cases of spontaneous fracture from such metastases. The author does not know whether or not the French radiologists are correct in their assumption that the insertion of radium is responsible for the occurrence of bone metastases. He agrees with them that too large doses of radium should not be used in order to avoid local trauma. He is convinced that neither operation (abdominal or vaginal) nor roentgen ray therapy produces skeletal metastases. In spite of the bad prognosis of bone metastases, x-ray or radium therapy should be carried out in order to lessen the severe pain in the periosteum which is associated with these metastases.

J. P. GREENHILL.

Masson, James C., and Gregg, Robert O.: Carcinoma of the Body of the Uterus, Surg., Gynec. & Obst. 70: 1083, 1940.

The histories of 907 patients suffering from malignant lesions of the body of the uterus seen at the Mayo Clinic from Jan. 1, 1910, to Dec. 31, 1933, inclusive, have been reviewed. Eight hundred eighty patients were treated and traced for five years or more. Seven hundred thirty-two patients were seen primarily at the clinic with definite carcinoma of the body of the uterus; 728 were treated. In 22 additional cases there was carcinoma of the body and cervix; in 18 more there was carcinoma of the body of the uterus and of the ovary, and in 1 there was carcinoma of the body of the uterus and a fibrosarcoma of the ovary. Forty-seven patients suffering from recurrent carcinoma after treatment elsewhere were seen at the clinic. Three cases of carcinoma and fibrosarcoma in the same specimen were found in the same period. Eighty-four patients suffering from sarcoma were seen in the same period, 82 of whom were traced for five years or more. An analysis of 732 cases of primary carcinoma of the fundus is presented in detail.

Two hundred twenty-one patients were premenopausal, 510 postmenopausal. The average age at menopause of the postmenopausal group was 50.27 years, that of a control group 49.9 years.

Metrorrhagia was complained of by 660 patients, or 90.2 per cent. Its average duration was eighteen months. An abnormal discharge was present in 502 patients, or 68.6 per cent. On the average it had persisted 16.4 months. Menorrhagia occurred in 119, or 56.1 per cent, of 212 premenopausal patients. It had lasted 49.6 months on the average. Pain occurred in 204 patients, or 27.9 per cent, persisting on the average for 13.2 months.

Leiomyomas of the uterus were associated with carcinoma of the fundus in 215 of 590 cases in which operation was performed, an incidence of 36.4 per cent.

Of 257 cases in which the histologic grade was determined, 57 were graded 1, 134 graded 2, 31 graded 3, and 35 graded 4.

In 467 cases which it was possible to classify as to stage of growth, there were 89 Stage 1, 217 Stage 2, 77 Stage 3, and 84 Stage 4.

stump cancer are due, according to the author, to an absence of the uterine body which may prevent the correct application of a sufficient dose of radium. Emphasis is again placed on the fact that an adequate dose of radium applied to the cervix is capable of controlling the disease only in and directly adjacent to the cervical tissues.

WILLIAM BERMAN.

Smith, George Van S., and Pemberton, Frank A.: Carcinoma of the Uterine Cervix, New England J. Med. 222: 481, 1940.

Of the 997 consecutive cases with a clinical diagnosis of cervical cancer, seen at the Free Hospital for Women clinic from May, 1876, to January, 1934, 69 had had their primary treatment elsewhere and 148 cannot now be proved to have had the disease. This paper discusses in detail from various angles the remaining 780 consecutive cases, previously untreated and pathologically confirmable, encountered from October, 1902, to January, 1934.

But a few of the several important conclusions drawn from a thorough analysis of this large series of cervical cancers, observed during a long period of time, can be quoted here. As previously stated by other authors, this study shows the necessity, as part of the follow-up regime, to include periodic investigation of the whole urinary tract. Clinical classification and pathologic grading prove practically valueless in the evaluation of therapy. Since improved results have been associated, first, with the use of radium and then with addition of supplementary x-radiation, the indications for surgery have become greatly restricted. The appreciable incidence of carcinoma in cervical stumps, also in nulligravidas, re-emphasizes the desirability of removal of the cervix with the uterus, if feasible. Retreatment for recurrence is salutary in but few instances. In this series, 67 per cent of those apparently free of disease at five years are found to be well at ten years after primary therapy. There were six unquestionable cases of multiple malignancy in this series.

HUGO EHRENFEST.

Auster, Lionel S., and Sala, Angelo M.: Causes of Death in Cancer of the Cervix Uteri, Surg., Gynec. & Obst. 71: 231, 1940.

Cancer of the cervix is amenable to successful treatment by radiation in various forms and combinations. The literature contains numerous authoritative and well-substantiated reports of five-year cures and over. Such results can be obtained only when adequate treatment is given to patients in the early stage of their disease, and then continuous follow-up observation and treatment maintained.

There has been no previous attempt to evaluate accurately the causes of failure in the therapy and the real cause of death of the greater number of even presumably well-treated patients.

Curative therapy is useless in clinical Stages 3 and 4 cases. Even though the local visible vaginal lesion may be banished and its recurrences controlled, most cases eventuate in necrosis with ulceration and severe local infection. The paramount difficulty in treatment is the control of the progressive damage to the urinary tract which is involved in almost all late cases. Superimposed infection results in an overwhelming majority of the cases and is the outstanding cause of death. Although infection of the urinary tract is the most important source of sepsis, peritonitis forms a large group which has not previously been sufficiently recognized since the process is frequently clinically silent.

Metastases of widespread character are not uncommon and should be noted more often in the future as therapeutic measures become more widespread in their application, resulting in longer life for these patients who, untreated, usually die within eighteen months. Bone metastases, both of hematogenous skeletal distribution and of direct contiguous pelvic type, will be noted as patients live long enough to develop them. Thoracic lesions are also to be noted.

Bilateral oophorectomy with total hysterectomy is the proper treatment. Involvement of the uterus, adhesions, and growth through the wall of a tumor are extremely dangerous.

The rupture of cysts before and during operation is condemned, but the results of this series cannot support the condemnation. It is the author's belief that spilling of cyst contents should be avoided.

X-ray treatment to date has not proved of much curative value but more modern methods may.

Every cystic or solid tumor of the ovary that is removed should be opened by the surgeon before the wound in the abdomen is closed.

If cancer is found in a single ovary by the pathologic department, resort should not be made to radiation but the patient should be re-operated upon and radical surgery carried out.

WILLIAM C. HENSKÉ.

Maizels, Gerald: Probable Chorionepithelioma in a Virgin of Seventy-One, *Lancet* 1: 690, 1940.

The author describes an abdominal tumor removed at autopsy from a 71-year-old virgin. The menopause had occurred twenty years previously, and no bleeding had been present until three months before death. Examination under anesthesia two weeks before death revealed an intact hymen with the vulva, cervix, and vagina consistent with virginity. A mass connected with the uterus reached halfway to the umbilicus.

The tumor proved to be a typical and highly malignant chorionepithelioma. Metastases were present in the lungs and liver.

The author suggests as the most reasonable explanation that the tumor originated from a teratoma of the uterus. Unfortunately the ovaries were not examined microscopically but both were grossly normal.

CARL P. HUBER.

Brown, Snodgrass, and Pratt: Latent Choriocarcinoma, *Am. J. Cancer* 38: 564, 1940.

Latency, the concealed retention of potentially or actually malignant cells in a dormant state over a long period of time, is a curious and important phenomenon which has been observed in numerous types of malignant tumors. Because of the foreign nature of the cells of the placental chorion, and the presumably easy establishment of the date of their origin, latent chorionepithelioma has attracted particular attention. Several series of such cases have been collected, showing occasionally a latency of over five years—in one instance a period of thirty years having passed between the last pregnancy and discovery of the tumor at the age of seventy.

To the small group of cases in which proof of latency is apparently conclusive, another is added, in this paper.

This patient was curetted in 1927 for a hydatiform mole. Two years later a total hysterectomy was done for continued severe uterine hemorrhages. No evidence of a new growth could be found in the specimen. She seemed perfectly well for next six years when (32 years old) she was admitted to the hospital for persistent productive cough, with hemoptysis for five months. An exploratory thoracotomy revealed a large mass in the upper half of the right lower lobe. Patient died eight weeks later. Autopsy showed typical choriocarcinoma through both lungs. No evidence of the tumor was found in the pelvis or in any of the pelvic or abdominal lymph nodes.

It seems clear from both clinical and pathologic findings that the final development of the tumor began in the right lung. The original source of the chorionic tissue seems undoubtedly to have been the vesicular mole, which represented the patient's last known pregnancy.

Only 59.6 per cent of Grade 1 lesions were postmenopausal, whereas 82.9 per cent of Grade 4 lesions occurred in the postmenopausal group. There was no significant difference in different grades as to discharge, anemia, or pain.

The hospital mortality for all treated patients suffering from pure carcinoma of the fundus was 38, or 5.22 per cent. Fourteen deaths were due to peritonitis and 12 to pulmonary emboli.

The five-year survival of 711 traced patients suffering from distinct carcinoma of the fundus was 425 cases, or 59.8 per cent. The ten-year survival of 520 traced patients was 252, or 48.5 per cent. The five-year survival of all patients having carcinoma of the fundus including those with carcinoma of cervix and ovary was 56.9 per cent. Omitting the recurrent cases, the five-year salvage was 59.4 per cent. The five-year survival of 86 traced Stage 1 patients was 72, or 83.7 per cent; of 210 traced Stage 2 patients, 74.3 per cent; and of 76 traced Stage 3 patients, 60.5 per cent; and of 49 traced Stage 4 patients on whom operation was performed, 24.5 per cent. The five-year survival of 57 Grade 1 traced patients was 77.2 per cent; of 134 Grade 2 patients, 64.9 per cent; of 31 Grade 3 patients, 61.3 per cent; and of 31 Grade 4 patients, 41.9 per cent. Six of 22 patients with carcinoma of the body and also of the cervix lived five years after treatment. Of 47 patients with recurrent pelvic carcinoma, probably arising in the body of the uterus, 8 were living five years after treatment.

Forty-two patients whose lesions were technically operable but who were irradiated alone because of their poor general condition gave a five-year salvage of 25, or 59.5 per cent, whereas the five-year survival of all patients with Stage 1, 2, or 3 growths on whom operation was performed was 73.1 per cent. The average age of the irradiated group, however, was 63.4 years, whereas the average age of the group operated upon was 55.5 years.

The occurrence of leiomyoma with carcinoma had little influence on the symptoms or prognosis in fundal carcinoma. Anemia was the single factor more common in patients with leiomyoma than in the rest of the group.

Eighty-four patients with sarcoma of the uterus were primarily treated at the Mayo Clinic in this period. Eighty-two of this group were traced five years. Of them 45, or 54.9 per cent, were living at the end of this period. The hospital mortality was 2 cases, or 2.4 per cent.

In 3 cases there were both sarcoma and carcinoma in the same specimen. Each case was in the Stage 2 classification, and each patient lived more than five years.

WILLIAM C. HENSKE.

Gunning, R. E. Lee, and Ross, Charles: *Rhabdomyosarcoma of the Corpus Uteri*, Surg., Gynec. & Obst. 70: 230, 1940.

Rhabdomyosarcoma signifies a tumor containing striated muscle cells of embryonic type. Rhabdomyosarcoma of the corpus uteri is very rare, only 10 cases having been reported to date. A new case, occurring in a 58-year-old woman ten years past the menopause, is described clinically and pathologically. A summary of all cases so far reported reveals the fact that these tumors occur in women past the menopause, that they are prone to metastasize, and that all contain embryonic forms of striated muscle cells.

WILLIAM C. HENSKE.

Meigs, Joe Vincent: *Cancer of the Ovary*, Surg., Gynec. & Obst. 71: 44, 1940.

Cancer of the ovary of the solid type is a very serious neoplasm.

Cancer of the ovary of the malignant papillary cystadenoma type is about as malignant as any other epithelial growth.

Early diagnosis and methods for early diagnosis are necessary to improve the end-results. The use of the peritoneoscope should prove of extreme value.

Items

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Cleveland, Ohio, by the entire Board from Wednesday, May 28, to Monday, June 2, 1941, inclusive, prior to the opening of the annual meeting of the American Medical Association in Cleveland.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reevaluation* in Part II must make written application to the Secretary's Office before April 15, 1941.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

"The Foundation Prize" of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons

Rules Governing the Award

(1) "The award which shall be known as 'The Foundation Prize' shall consist of \$150.00.

(2) "Eligible contestants shall include only (a) interns, residents, or graduate students in Obstetrics, Gynecology or Abdominal Surgery, and (b) physicians (with an M.D. degree) who are actively practicing or teaching Obstetrics, Gynecology or Abdominal Surgery.

(3) "Manuscripts must be presented under a *nom-de-plume*, which shall in no way indicate the author's identity, to the Secretary of the Association together with a sealed envelope bearing the *nom-de-plume* and containing a card showing the name and address of the contestant.

(4) "Manuscripts must be limited to 5,000 words, and must be typewritten in double-spacing on one side of the sheet. Ample margins should be provided. Illustrations should be limited to such as are required for a clear exposition of the thesis.

(5) "The successful thesis shall become the property of the Association, but this provision shall in no way interfere with the publication of the communication in the journal of the author's choice. Unsuccessful contributions will be returned promptly to their authors.

(6) "Three copies of all manuscripts and illustrations entered in a given year must be in the hands of the Secretary before June 1st.

(7) "The award will be made at the Annual Meetings of the Association, at which time the successful contestant must appear in person to present his contribution as a part of the regular scientific program, in conformity with the rules of the Association. The successful contestant must meet all expenses incident to this presentation.

(8) "The President of the Association shall annually appoint a Committee on Award, which, under its own regulations shall determine the successful contestant and shall inform the Secretary of his name and address at least two weeks before the annual meeting."

For further information, address Jas. R. Bloss, M.D., Secretary, 418 Eleventh Street, Huntington, W. Va.

It might be assumed and seems most plausible that simple pulmonary embolism of benign molar tissue occurred during the original curettement, with malignant change taking place only years later.

HUGO EHRENFEST.

Brewer, John I.: Kraurosis and Leucoplakia of the Vulva, Illinois M. J. 77: 26, 1940.

Kraurosis vulvae is a condition of the skin most frequently seen in the region of the clitoris, labia minora, perineum, and labia majora. The lesion is white and the tissues appear shrunken but in some instances edema may produce a thickened skin. Fissures and ulcerations are frequently encountered. The author denies the statement that all atrophic lesions of the vulva with shrinkage as observed grossly are to be classified as kraurosis vulvae and uses senile atrophy as an example to prove his case. He also differs with Taussig, stating that it is not necessary for hypertrophic epithelial changes to precede the kraurosis.

Leucoplakia is described as a gray, blue, gray white, or white lesion of the vulva. The skin appears thickened. Fissures and ulcerations occur.

Leucoplakia and/or kraurosis are seen in association with all cancers of the vulva and because of this fact treatment should consist of a complete vulvectomy. Other forms of treatment such as endocrine therapy, nerve resection, hydrochloric acid, and vitamin A therapy may bring about temporary improvement only, and it seems unwise to use these measures in lesions which are so frequently associated with cancer.

EUGENE S. AUER.

Sparrow, Thomas D.: Leukoplakic Vulvitis, Ann. Surg. 112: 87, 1940.

The author reviews the literature of leukoplakic vulvitis, and refers to the various names which have been given to somewhat related conditions, such as, kraurosis vulva and atrophic vulvitis. He reports 6 cases of his own. After all of the confusion is cleared up concerning the etiology of this condition, the most important factor seems to lie in ovarian dysfunction, or cessation of hormonal activity. He feels that there are probably other factors which as yet are unknown to us. Normally ovarian hormone exerts some protective influence over the genital skin, and in certain women withdrawal of the hormone results in an inflammatory process with leucoplakia and kraurosis as its principal gross manifestations. The pathologic processes from the primary swelling and hypertrophic changes to the atrophic stages are reviewed.

He points out that treatment with vitamin A, hydrochloric acid, and hormones have proved unsuccessful, and he feels that surgery is the best choice of treatment. It relieves the distressing symptoms and eradicates a definitely precancerous condition. Surgery was used in all 6 cases reported, with malignancy in 1 case. Post-operative complications occurred in all but 1 case. These consisted chiefly in a recurrence of subjective symptoms. Four of these patients were treated with estrogenic ointment (Foss) with some relief of the symptoms.

WILLIAM BERMAN.

- New England Obstetrical and Gynecological Society.** *President*, Frederick L. Good. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** *President*, John Vruwink. *President-Elect*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting, Los Angeles, Calif., November 5 to 8, 1941.
- Washington Gynecological Society.** *President*, R. L. Sylvester. *Secretary*, W. R. Thomas, 1830 K. Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, E. L. Zander. *Secretary*, Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, E. Lee Dorsett. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Henshaw Kelly. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, Roy Grogan. *Secretary*, J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Galveston, Texas, September, 1941.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, Russell W. Allen. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Francis R. Irving. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, T. M. Boulware, Birmingham, Ala. *Secretary*, Eva F. Dodge, 519 Dexter Avenue, Montgomery, Ala. Next meeting, Mobile, Ala., April, 1941.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.

Books Received

DIAGNOSIS AND TREATMENT OF MENSTRUAL DISORDERS AND STERILITY. By Charles Mazer, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, etc., and S. Leon Israel, M.D., F.A.C.S., Instructor in Gynecology and Obstetrics, School of Medicine, University of Pennsylvania. With 108 illustrations, 485 pages. Paul B. Hoeber, Inc., New York City, 1941.

PHARMACOLOGICAL BASIS OF THERAPEUTICS. By Louis Goodman, M.A., M.D., Assistant Professor of Pharmacology and Toxicology, Yale University, School of Medicine, and Alfred Gilman, Ph.D., Assistant Professor of Pharmacology and Toxicology, Yale University, School of Medicine. 126 figures, 1383 pages. The Macmillan Company, New York, 1941.

TECHNIQUES OF CONTRACEPTION CONTROL. By Robert Latou Dickinson, M.D., and Woodbridge Edwards Morris, M.D., General Medical Director, Birth Control Federation of America. 50 illustrations, 56 pages. The Williams & Wilkins Company, Baltimore, 1941.

WILLIAMS OBSTETRICS. By Henricus J. Stander, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Cornell University Medical College, etc. Eighth edition, 704 illustrations, 1401 pages. D. Appleton-Century Company, Inc., New York, 1941.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(*Appears in January, April, July, October*)

- American Gynecological Society.** *President*, E. J. Litzenberg. *Secretary*, Richard W. TeLinde, 11 East Chase Street, Baltimore, Md. Next meeting, May 26 to 28, 1941, Broadmoor Hotel, Colorado Springs, Colo.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, Frederick H. Falls, Chicago, Ill. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting will be held at the Homestead, Hot Springs, Va., September 11 to 13, 1941.
- Central Association of Obstetricians and Gynecologists.** *President*, Thomas B. Sellers, New Orleans, La. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Next meeting, New Orleans, La., Fall of 1941.
- South Atlantic Association of Obstetricians and Gynecologists.** *President*, R. A. Bartholomew, Atlanta, Ga. *Secretary*, Robert A. Ross, Durham, N. C. Next meeting, February, 1942, Atlanta, Ga.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Norman F. Miller, Ann Arbor, Mich. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June 2 to 6, 1941, Cleveland, Ohio.
- New York Obstetrical Society.** *President*, Thomas C. Peightal. *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** *President*, Roy W. Mohler. *Secretary*, John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** *President*, Harold K. Gibson. *Secretary*, James A. Gough, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** *President*, George G. Cochran. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** *President*, Abraham Samuels, *Secretary-Treasurer*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society.** *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Robert F. Monroe. *Secretary*, Layman A. Gray, 332 West Broadway, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** *President*, S. A. Chalfant. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** *President*, John Rock. *Secretary*, Judson A. Smith, 264 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

has been considered the common etiologic factor (Witherspoon, 1933 and 1935, and others).

7. Failure of ovulation has been reported by many (Witherspoon, 1933; Burch and Burch, 1933; Albrecht, 1935; and Popow, 1890).

8. The frequent finding of multiple follicular cysts in the ovaries has suggested the possibility of excessive estrin production (Witherspoon, 1933; Burch and Burch, 1933; Albrecht, 1928; Popow, 1890).

9. Endometriosis and adenomyosis are frequent concomitant lesions with uterine fibroids. Since these lesions occur only during the active life of the ovaries, the importance of the ovarian hormone as a common etiologic agent is assumed (Smith, 1929; Allen, 1933; Witherspoon, 1935).

It must be noted here, however, that most of the above statements have been subjected to criticism.

R. Meyer (1930) believed that the growth of fibroids was dependent on the ovary, principally because active ovarian function was associated with increased blood supply to the pelvic tissues. Dichtl (1938) demonstrated that fibroids might grow after the menopause in the presence of extensive vascular adhesions. The rapid growth of fibroids during pregnancy is, in many instances at least, not a true growth but rather an enlargement due to edema, degenerative changes, and increased blood supply. R. Meyer (1930) stressed the fact that many patients with fibroids menstruated and ovulated normally and became pregnant. Cystic ovarian changes were present in no unusual frequency in patients with fibroids (Häggstrom, 1932). Curtis (1938) suggested that the sterility was dependent upon an interference with the development and delivery of the fetus rather than the prevention of conception.

Experimentally, it has been reported that fibromyomas have been produced in the guinea pig as a result of the administration of large doses of estrogens over a long period of time (Nelson, 1937; Dessau, 1938; Moricard and Cauchoix, 1938; Lipschutz and Iglesais, 1938). Lacassagne (1935) reported that he was able to produce myometrial fibromas in the rabbit by prolonged administration of the estrogenic hormone. In all other experimental animals such as the mouse, rat, and monkey all efforts to produce fibroids have failed.

The foregoing remarks indicate that estrin, as a single etiologic factor, may be very important, but that, as yet, definite proof has not been established.

The study reported in this paper was undertaken to give the authors a personal knowledge of the ovarian function and endometrial relationship in 100 unselected and consecutive patients operated upon for uterine fibroids.

MATERIAL AND METHODS

This study is based upon two extremely important facts; namely, that preparations and plans were completely thought out before the collection of specimens was begun, and that the patients were unselected and consecutively operated upon. There was no attempt made to choose the time of the cycle at which to operate upon the patients. In this way, the study more truly portrays the actual findings in 100 patients with uterine fibroids.

It was decided that 100 specimens of uterine fibroids with histologic preparations of the endometria and the ovaries would be adequate material and that more than this number would make the material too unwieldy to study individually and personally with the maximum efficiency. The collection of specimens required one year's time.

One of us or our assistant, Mrs. Laird, was required to be present at each operative procedure. A description of the operative findings was written at once. The number, position, and size of the fibroids, size of the ovaries and the character of

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Original Communications

A STUDY OF THE CORPORA LUTEA AND THE ENDOMETRIUMS IN PATIENTS WITH UTERINE FIBROIDS*

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INTRODUCTION

THE etiology of uterine fibroids is unknown. The most generally accepted theory at the present time proposes the etiologic importance of estrin. Excessive stimulation of the myometrial tissues by either hyperestrinism or the unopposed action of estrin results in this tumor formation according to many authors. Proof given to establish this theory consists of both experimental and clinical facts and interpretations.

Clinically, the existence of a close relationship between ovarian function and the development of uterine fibroids has been accepted. This conclusion was based upon the following:

1. Fibroids develop only during active ovarian life.
2. Fibroids usually cease to grow after the menopause or after castration.
3. Fibroids grow rapidly during pregnancy.
4. Sterility in patients with fibroids is thought to be dependent upon disturbed ovarian function (Freund, 1913; Albrecht, 1928).
5. Abnormal uterine bleeding is a common symptom of patients with fibroids. The bleeding is considered to be the result of ovarian dysfunction (Graves, 1930).
6. Cystic glandular hyperplasia has been reported frequently in such patients. Hyperplasia results from excessive or prolonged estrogenic stimulation. Thus, estrin

*Presented at a meeting of the Chicago Gynecological Society, January 17, 1941.

Aided by a grant from the Albert B. Kuppenheimer Fund of St. Luke's Hospital.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

in only one instance and that was in a patient operated upon on the fourteenth cyclic day (Patient 9). The corpus luteum was young. The granulosa cells were not completely luteinized. There was a very meager amount of connective tissue in the granulosa cell layer. A connective tissue lining of the central cavity was absent. The theca cells contained many vacuoles from which lipoids had been dissolved during the process of fixation. The endometrium was early pro gravid.

Several patients had demonstrable degenerating corpora lutea of the immediately previous cycle and some had large mature follicles. The endometriums in the patients without corpora lutea were proliferative in type and were similar to the endometria removed at similar times in the cycle from normal women and *Macacus rhesus* monkeys (Bartelmez, 1933; Markee, 1936). There was no cystic glandular hyperplasia present.

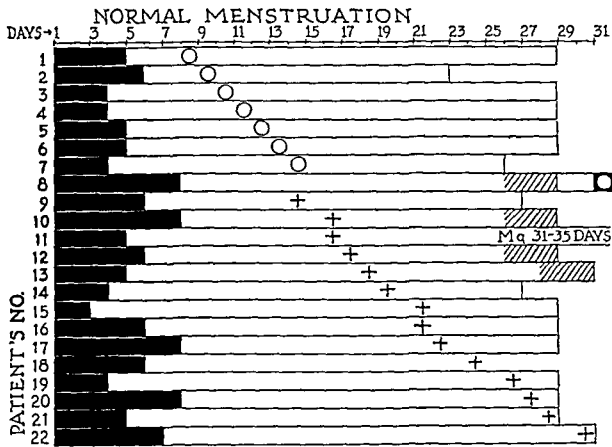


Fig. 1.

Figs. 1 to 5.—In all the charts the days of the menstrual cycle are arranged horizontally. The patients' numbers are listed vertically. The last menstrual cycle of each patient is portrayed in the horizontal columns. The solid black portion represents the bleeding phase of the cycle. In those patients operated upon before the menstrual flow has ceased, the solid black portion indicates the usual anticipated length of flow. The terminal bar at the end of the column indicates the length of the menstrual cycle. The diagonal lines indicate the variability in the length of the cycle in an individual patient. The zero indicates both the day of the menstrual cycle the patient was operated upon, and the absence of a functioning corpus luteum of the present cycle. The plus sign indicates the presence of a functioning corpus luteum of the present cycle as well as the day of the cycle the patient was operated upon.

Fourteen patients were operated upon after the sixteenth day of the cycle (Fig. 1). Thirteen had functioning corpora lutea of the present cycle. One patient (Patient 8, aged 44 years) without a corpus luteum was operated upon on the thirty-first day of her cycle, just as menstruation was beginning. The endometrium was proliferative in type and some desquamation had occurred. A corpus luteum could not be demonstrated grossly. Tissues were available for microscopic study from only one ovary. It is probable that this represents an instance of cyclic anovulatory bleeding, but one cannot prove this, since both ovaries were not sectioned serially.

The corpora lutea in the two patients (Patients 10 and 11) operated upon on the sixteenth day differed in degree of development. One (Patient 10) was typical of the early vascularization stage, while the other was distinctly younger (Patient 11). The endometrium of Patient 10 showed the greater degree of stimulation. It is interesting to compare the menstrual histories of the 2 patients. The cycle of Patient 11 was thirty-one to thirty-five days as compared to that of Patient 10 which was twenty-six to twenty-eight days. Ovulation had undoubtedly taken place later in the cycle in that patient with the longer cycle. This is consistent with the phenomenon as it occurs in entirely normal women.

the follicles, corpora lutea, and the concomitant pelvic pathology were recorded. Several blocks of endometrium from various portions of each uterus were fixed in aqueous-formol-chrome-sublimite. Portions of the corpora lutea were fixed in aqueous-formol-chrome-sublimite and various other fixations for cytologic studies. The tissues were embedded in paraffin and cut at five microns. Mallory connective tissue stain and acid fuchsin-methyl green stain were used.

Throughout the study, only the functioning corpus luteum of the cycle that is being observed will be considered and counted. Many patients had a corpus luteum of the immediately preceding cycle, but they are not to be considered, because of our desire to rigidly limit the study to the present cycle as nearly as possible.

The cytologic descriptions will be published later. All tissues were fixed within five minutes after the blood supply was clamped. In some instances, the ovary containing the corpus luteum was not removed but the corpus luteum was dissected out for histologic study.

An accurate menstrual history was obtained from each patient, and when some doubt existed, the menstrual dates were checked again immediately. In this manner, a survey of hospital records months afterwards was obviated.

The 100 patients ranged in age from 26 to 52 years. Four were from 26 to 29 years of age, eight from 30 to 34, thirty-eight from 35 to 39, twenty from 40 to 44, twenty-six from 45 to 49, and four from 50 to 52 years of age.

The patients were grouped according to the character of their menstrual cycles. Twenty-two patients had no variation from their normal cycles (Fig. 1). In all of these patients the menstrual cycles were within the limits given for normal. Twenty-six patients complained of menorrhagia. Fifteen of these had such a slight increase in flow that the cycles were still within normal limits. For this reason they are considered as a separate group (Fig. 2). Eleven patients had menorrhagia sufficiently severe to disturb their usual menstrual rhythms (Fig. 3). The menstrual history of Patient 46, for example, appears within normal limits in Fig. 3. The flow of four days' duration was characterized by the patient as a hemorrhage which was at variance with her previous normal period. For this reason she is considered in this group. In other instances the charts of patients with irregular and abnormal bleeding indicate that the present cycle is normal. As nearly as possible, the data presented in the charts are those of the single menstrual cycle about the time of operation. It is frequently observed that a patient with abnormal bleeding may have a completely normal cycle interspersed with an abnormal cycle. Thus, while the single cycle studied and charted may be normal, the patient is grouped according to the predominant type of bleeding complained of.

A group of 8 patients complained only of metrorrhagia (Fig. 4). Thirty-five patients had both metrorrhagia and menorrhagia (Fig. 5). Amenorrhea, partial or complete, was present in four patients. One patient had oligomenorrhea. Three patients were pregnant at the time of operation and one other patient had a chorio-epithelioma. Each group will be studied and discussed individually.

GROUP I. NORMAL MENSTRUATION

The 22 patients in this group ranged in age from 29 to 46 years (Fig. 1). The average age was 39 years. Concomitant pelvic pathology was present in 13 patients (residues of pelvic infection, 5; bilateral dermoid cysts, 1; papillary cystadenoma, 1; and endometriosis, 6). Only one patient possessed ovaries with follicular cysts. The largest was 2 cm. in diameter and only 3 were present. The ovaries of the patients in this group were normal in size, except in the instance of the patient with the dermoid cysts.

Seven of the 22 patients were sterile. Three had no pelvic pathology other than the fibroids, while 2 had residues and 2 had endometriosis. One of the 22 patients had never married and had had no pregnancies.

Ten patients had had 23 full-term pregnancies and 3 miscarriages. Four patients had been pregnant but had never completed full-term pregnancies.

Eight patients of this group were operated upon on or before the fourteenth day of their cycles (Fig. 1). There was a corpus luteum of the present menstrual cycle

the corpus luteum was removed earlier in the cycle in the case of the former. Desquamation of portions of the endometrium had occurred while the endometrium in Patients 21 and 22 evidenced involution in one instance and a late progravid stage without involution in the other. The close relationship between the character of the corpus luteum and the changes in the endometrium as noted here is identical to that observed in the tissues of normal women.

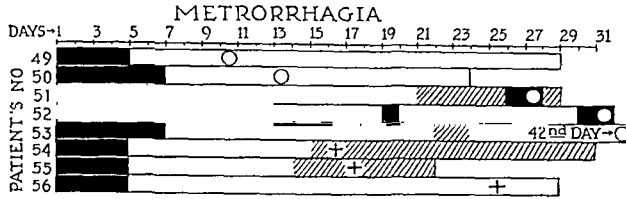


Fig. 4.

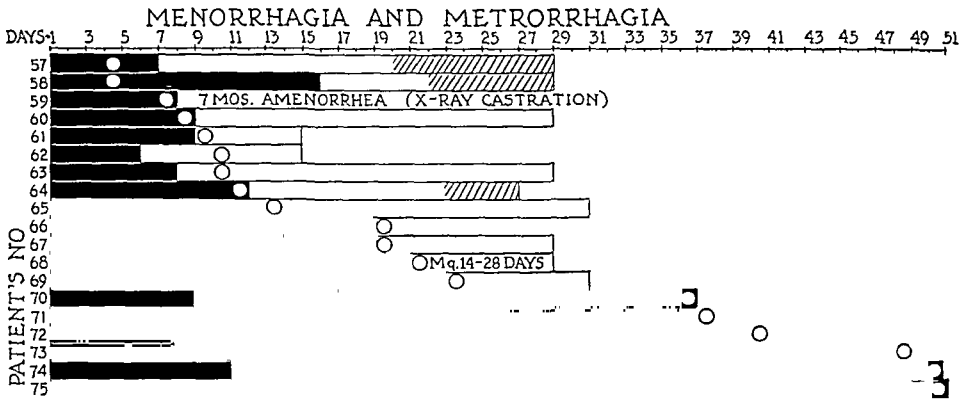


Fig. 5, A.

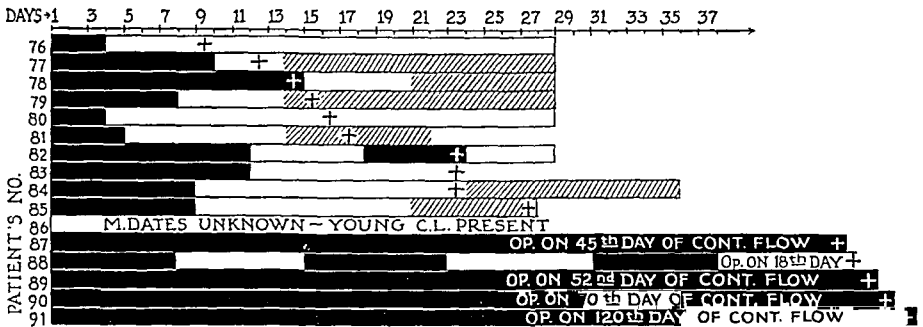


Fig. 5, B.

Such findings suggest strongly that there is no disturbance in the ability of the follicle and the corpus luteum to stimulate the endometrium normally and the endometrium to respond normally in this group of patients with uterine fibroids. The endometriums showed no hyperplasia or any undue or abnormal estrogenic stimulation.

Ovulation had occurred and the development of the corpus luteum through its life cycle had progressed similarly in all instances to these phenomena as they occur in normal women.

The corpora lutea removed on the seventeenth and eighteenth days of the cycles, respectively (Patients 12 and 13), were in the vascularization stage. The endometriums were early progravic in character.

All of the corpora lutea removed after the nineteenth cyclic day were in the so-called bloom stage. The endometrium in each instance evidenced the normally anticipated degree of stimulation. In Patient 15 the corpus luteum was 3 cm. in diameter and was cystic. The characteristic folds of the walls were absent. The cells appeared normal in all respects. The endometrium was normally stimulated. The cystic condition of the corpus luteum had apparently not altered its normal physiologic function.

Patient 21 was operated upon on the twenty-eighth day. Her normal cycle was twenty-eight days in length. The late progravid endometrium had not evidenced any involution, and menstruation was not imminent. The corpus luteum showed no signs of disintegration and was in a typical bloom stage. This cycle, while normal, was to be of greater length by several days than the usual.

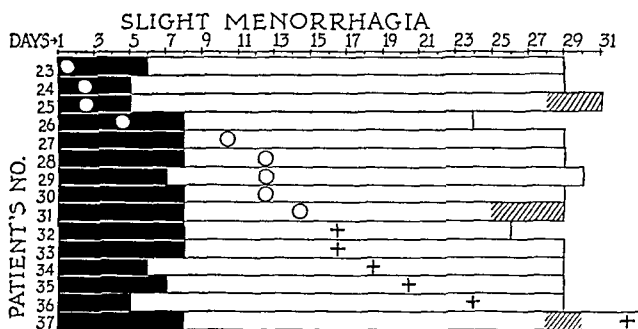


Fig. 2.

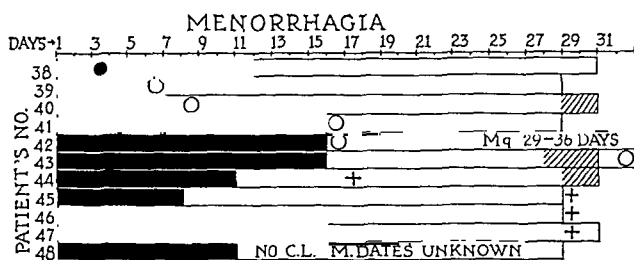


Fig. 3.

Patient 22, operated upon on the thirtieth day of her usual thirty-day cycle, possessed an endometrium in which involution had begun. The edema had largely disappeared and the glands were collapsed. There was a broad compacta filled with typical decidua cells. Such decidua may occur in the normal endometrium in the absence of pregnancy. The granulosa lutein cells were markedly degenerated in some portions, while in others the cells were typical of the late bloom stage. The corpus luteum was apparently undergoing degenerative changes prior to and more rapidly than the endometrium was evidencing the disintegration which typifies menstruation. This finding is consistent with that observed in the tissues of normal women.

The endometrium of Patient 18, removed at the end of the twenty-fourth cyclic day, showed beginning slough (Fig. 6). This patient's cycle was twenty-four days in length. The corpus luteum was degenerated for the most part (Fig. 7) but some small portions were still in the stage of bloom (Fig. 8).

The regression of the corpora lutea in Patients 18, 21, and 22 was of various degrees. It was more extensive in Patient 18 than in Patients 21 and 22, although

and the other had a small parovarian cyst. The sterility might readily have been the result of the concomitant pathology rather than the fibroids, since these pathologic lesions preceded the fibroids by many years.

Five patients had 21 pregnancies. Twelve terminated by full-term deliveries and 9 resulted in miscarriages. One of the 11 patients had never delivered a full-term pregnancy but had had 5 miscarriages.

It is in this group of patients with abnormal bleeding that some irregularities in the normal cyclic behavior of the ovaries and endometriums were observed. Patient 41 and patient 42, operated upon on the sixteenth day just at the termination of fifteen days of bleeding in each instance, possessed no corpora lutea of the present cycle. That ovulation would not have occurred during this cycle, however, cannot be stated, since there is a large, normal, mature follicle in one ovary of each patient. The endometrium in each instance was of an immediately postmenstrual type.

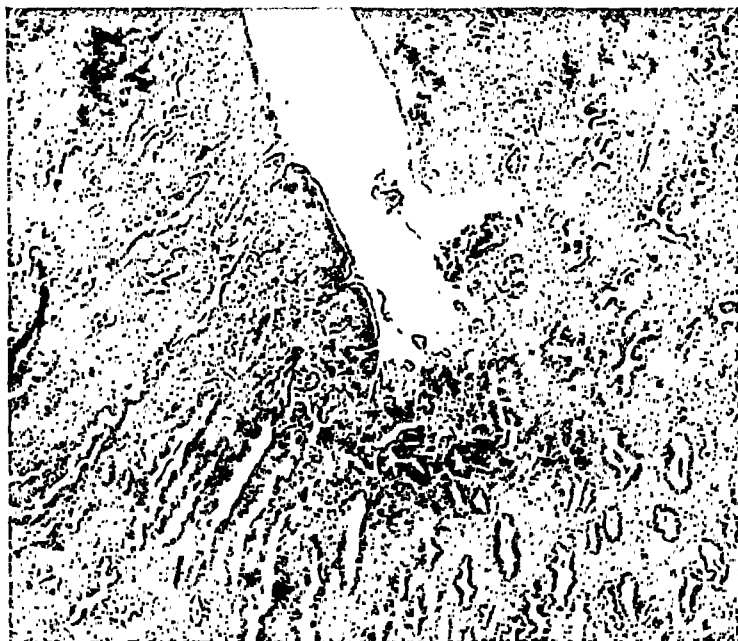


Fig. 6.

Figs. 6, 7, and 8.—Patient 18. Twenty-four-day cycle. Patient was operated upon as flow was beginning. Early desquamation of a small portion of the endometrium is shown. In Fig. 7 marked degeneration of the granulosa lutein cells is evident. Theca lutein cells are indicated by the arrow. Portions of the granulosa lutein cells had not undergone regression (Fig. 8). This demonstrates that the relationship between the corpus luteum and the endometrium is normal.

Patient 43 was operated upon on the thirty-second cyclic day. The usual cycle was twenty-eight to thirty days in length. No bleeding had occurred, however, and there was no indication found in the endometrium that menstruation would occur in the near future. The endometrium was a normal, proliferative type. The ovaries contained no corpus luteum. This patient, aged 49 years, had had two short periods of amenorrhea in the two years preceding the operation. Although she had no hot flushes, the amenorrhea and her age suggest an approaching menopause which might account for the failure of ovulation.

Patient 48 could give no dates concerning her menstrual periods. The ovaries contained no corpus luteum, and the endometrium was a proliferative type.

All of the remaining patients of this group had ovarian and endometrial findings that were consistent with those considered normal for the time of the cycle in which they were operated upon.

GROUP II. SLIGHT MENORRHAGIA

The 15 patients of this group complained of a menorrhagia so slight that it did not alter the cycles beyond the accepted limits of normal (Fig. 2). Their ages ranged from 26 to 49 years with an average age of 43 years. Concomitant pelvic pathology was present in eight instances (residues 7, and endometriosis 1). Three patients had never been married and twelve were married. Three of the 12 patients had never been pregnant, and in each, residues of pelvic infection were present which might have accounted for their sterility. Nine of the 12 who had become pregnant had completed 18 full-term pregnancies and only 1 had had a miscarriage.

The ovaries were of normal size in all but 3 patients of this group (Patients 23, 30, and 37). The cysts that produced the enlargements were follicular in 2 patients and a cyst of the corpus luteum in the other (Patient 37).

Nine of the 15 patients comprising this group were operated upon on or before the fourteenth day of the menstrual cycle. None possessed functioning corpora lutea of the present cycle. In most instances, corpora lutea of the previous cycle were identified.

The endometrium in each instance was stimulated to the degree that is considered normal for the stage of the cycle in which the tissue was removed. No cystic glandular hyperplasia was present.

Six patients were operated upon after the fourteenth day. In each a histologically normal corpus luteum was present. That the corpora lutea were functioning normally was indicated by the degree of the stimulation of the endometrium. The usually accepted normal relationship between the endometrium, the ovarian follicles, and corpus luteum existed here. Some slight variation was present in the tissues of Patient 37. This patient's usual cycle was twenty-eight to twenty-nine days in length. In the present cycle, however, she had failed to menstruate at the expected time and had not yet begun to flow when she was operated upon on the thirty-second day. The endometrium was early progradiv. The corpus luteum was 2.5 cm. in diameter and the folds were not as prominent as usually observed. The cells, however, were histologically normal. The stage of the corpus luteum was typical of an early bloom phase. The degree of stimulation of the endometrium was consistent with the extent of the development of the corpus luteum. Such findings might represent an instance of ovulation occurring late in the cycle. All the histologic evidences found in these tissues indicate them to be within normal limits, both anatomically and physiologically.

In this group of 15 patients with slight menorrhagia, the findings reduplicated those observed in the first group of normally menstruating patients and in normally menstruating patients without any pelvic pathology. In no instance in either of the groups did the character of the endometrium and the ovarian findings indicate any evidence of excessive, prolonged, or unopposed estrogenic stimulation.

There was no failure of ovulation in any of these patients. The corpora lutea were normal and the endometria had responded to corpus luteum stimulation in a normal manner. No so-called glandular hyperplasia was present. There was no disturbance from the normal in the ovarian and endometrial relationships in these patients.

GROUP III. MENORRHAGIA

Eleven patients complained of menorrhagia severe enough to disturb their menstrual rhythms (Fig. 3). In many instances normal cycles were interspersed among the abnormal ones. The ages of these patients ranged from 35 to 49 years, with an average age of 39 years. Concomitant pelvic pathology was present in 9 of the 11 patients (residues, 6; endometriosis, 1; endometriosis and residues, 1; parovarian cyst, 1). Follicular cysts were present in the ovaries of 4 patients. The largest was 6 cm. in diameter and in the other instances the measurements were 4, 2, and 2 cm., respectively. The sizes of the ovaries containing these cysts were only slightly greater than normal, with the exception of the one containing the 6 cm. cyst. The ovaries of the remaining patients were normal size.

Ten of the 11 patients were married. Four had never been pregnant. Two of these patients with sterility had residues of pelvic infection, one had endometriosis,

The 2 patients operated upon on the second day of the menstrual flow had degenerating corpora lutea and were menstruating from a previously prepared, normal, gravid endometrium. The other patients, with the exception of Patient 53, showed completely normal ovarian and endometrial relationship (Fig. 4). That a patient 50 years of age (Patient 53) should fail to ovulate and menstruate on the expected day is not distinctly abnormal.

The ovarian and endometrial findings in these patients are consistent with those in normal women. The single cycles studied in these patients were relatively normal, although a history of metrorrhagia occurring in some cycles was obtained from each patient.

GROUP V. MENORRHAGIA AND METRORRHAGIA

There were 35 patients who had both menorrhagia and metrorrhagia. Their ages were from 31 to 47 years with an average age of 40 years at the time of operation. Concomitant pelvic pathology was present in 20 of these patients (residues of pelvic infection, 14; endometriosis, 4; residues and endometriosis, 1; parovarian cyst, 1).



Fig. 9.

Figs. 9, 10, and 11.—Patient 78. Bleeding which began as a regular menstrual period had continued for fourteen days when the patient was operated upon. A portion of the corpus luteum in the regression phase is shown in Fig. 9. Fig. 10, taken at the same magnification, shows granulosa lutein cells typical of the bloom stage. The endometrium shown in Fig. 11 has a denuded surface. The endometrial glands are secretory in type in some portions of the endometrium and in others are typical of a proliferative stage (arrows). These figures demonstrate irregular regression of the corpus luteum and the associated shedding of the endometrium.

Follicular cysts were present in the ovaries of 9 patients. In 2, the cysts were 6 and 8 cm. in diameter, respectively. In the others the cysts were 2 cm. or less in size. A 5 cm. corpus luteum cyst was present in one instance (Patient 89). The size of the ovaries in the remaining patients of this group were normal.

Two patients had never married and had had no pregnancies. Seven patients had never been pregnant. One had residues of pelvic infection, 3 had endometriosis, and 3 had no concomitant pelvic pathology.

Twenty-six patients had been pregnant. Nineteen of these had completed 40 full-term pregnancies and had also had 9 miscarriages. Seven of the 26 patients who had been pregnant failed to carry a pregnancy to term and had had 18 miscarriages.

Nineteen of the 35 patients in this group had no corpora lutea of the present cycle (Fig. 5, A). Several, however, had normal corpora lutea of the previous cycle

GROUP IV. METRORRHAGIA

Eight patients complained of metrorrhagia (Fig. 4). No variations in the length of their cycles had occurred. The metrorrhagia was not present in every cycle, but the patients were placed in this group because metrorrhagia was complained of during the few months prior to operation. The ages ranged from 35 to 52 years, with an average age of 42 years at the time of operation.

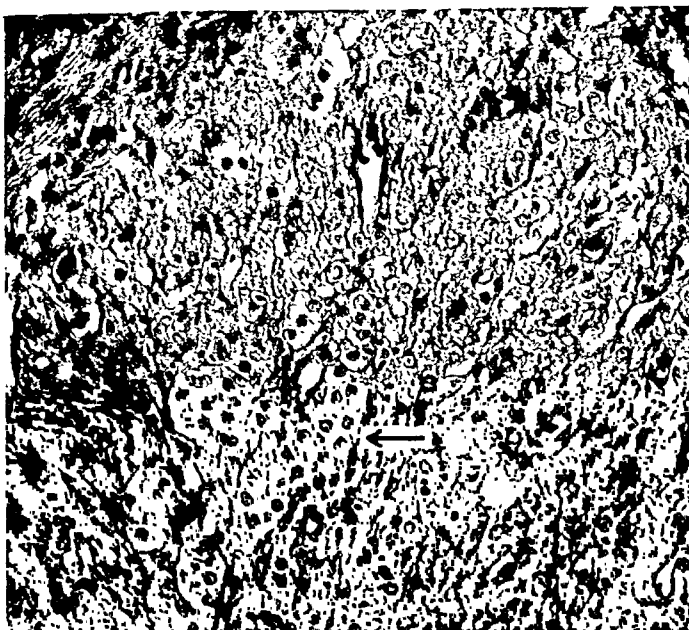


Fig. 7.

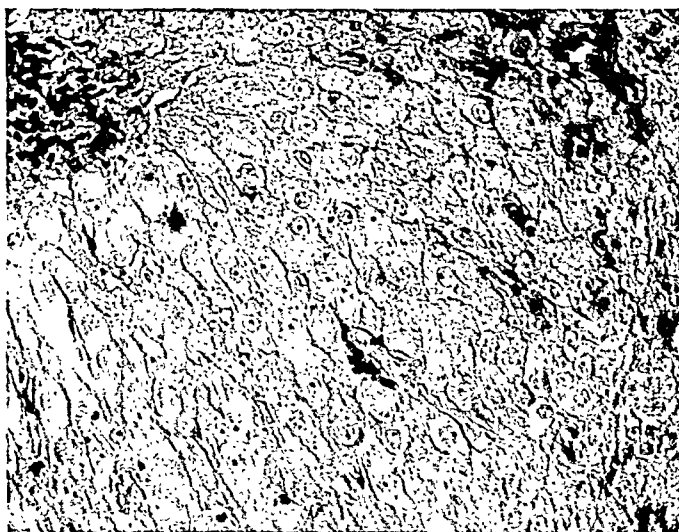


Fig. 8.

Three patients had concomitant pelvic pathology (residues of pelvic infection, 2; endometriosis, 1). The ovaries of the 8 patients were normal in size and in none were there any follicular cysts.

Two of the 8 had never been married. Two patients had had no pregnancies. Of these 2, one had endometriosis and the other had no concomitant pelvic pathology. Two patients had completed 2 full-term pregnancies. The remaining 2 patients had been pregnant four times but each pregnancy had terminated by a miscarriage.

Patient 74, aged 43 years, was operated upon on the second day of flow, following a cycle of fifty days in length (Fig. 5, *B*). The endometrium was proliferative in type without evidence of previous pro gravid character and had desquamated to a moderate extent. No corpus luteum was found.

In this group of patients without functioning corpora lutea of the present cycle, there was cystic glandular hyperplasia of the endometrium in only one instance (Patient 73). The hyperplasia was not marked.

Sixteen patients who complained of menorrhagia and metrorrhagia had corpora lutea. Of the 35 patients with menorrhagia and metrorrhagia, approximately half had corpora lutea, irrespective of the bleeding. In many instances the patients were operated upon during a relatively normal cycle (Patients 76, 79, 80, 81, 84, 85, and 88). In these patients the appearance of and the relationship between the corpora lutea and the endometria were normal. Similar normal findings and relationship existed in some of the patients with abnormal cycles (Patients 77, 82, and 83).



Fig. 12.

Figs. 12, 13, and 14.—Patient 87 had continuous bleeding for forty-five days. The endometrium pictured in Fig. 12 shows a localized region of disintegration and slough, adjacent to which is a region showing response to corpus luteum stimulation. It is not entirely normal, however. In other portions of the uterus the endometrium is typical of the proliferative phase (Fig. 13). In Fig. 14 the corpus luteum obtained from this patient is characteristic of the "bloom" stage. It is normal histologically. These findings suggest that the end organ (endometrium) is unable to respond in a normal manner to corpus luteum stimulation.

Patient 76 who was operated upon on the ninth day had a normal corpus luteum in the vascularization stage. Ovulation must have preceded operation by at least three or four days. Thus, in this patient ovulation occurred on or about the sixth day. Ovulation early in the cycle has been observed occasionally in normal women. The endometrium was pro gravid in character and consistent with the degree of development of the corpus luteum.

Irregular shedding of the endometrium occurred in Patient 78 (Table I). The granulosa lutein cells of the corpus luteum, removed on the fourteenth day of the present cycle, had undergone regression in some regions (Fig. 9), but in others the cells were typical of the bloom stage (Fig. 10). Active functioning cells such as these are not normally present in a regressed corpus luteum of the previous menstrual cycle. The endometrium had desquamated in most regions but the pro gravid character was still discernible (Fig. 11). It is probable that the irregular shedding of the endometrium was due, in this instance, to irregular regression of the corpus luteum.

In 4 patients (Patients 87, 89, 90, and 91) several unusual findings were observed. Patient 87 had been bleeding continuously for forty-five days. A small portion

in stages of regression (Patients 57 and 58, for example). Although these findings are not used in this paper, they do indicate that ovulation and corpus luteum development had occurred in the previous cycle.

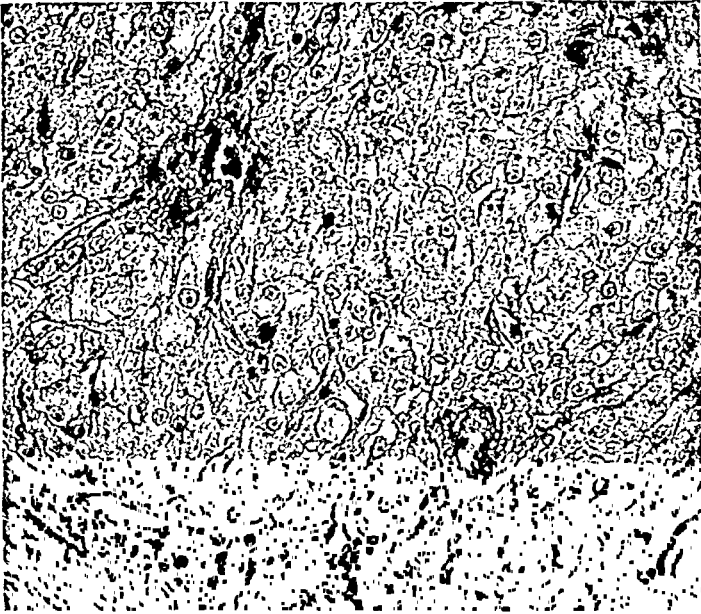


Fig. 10.

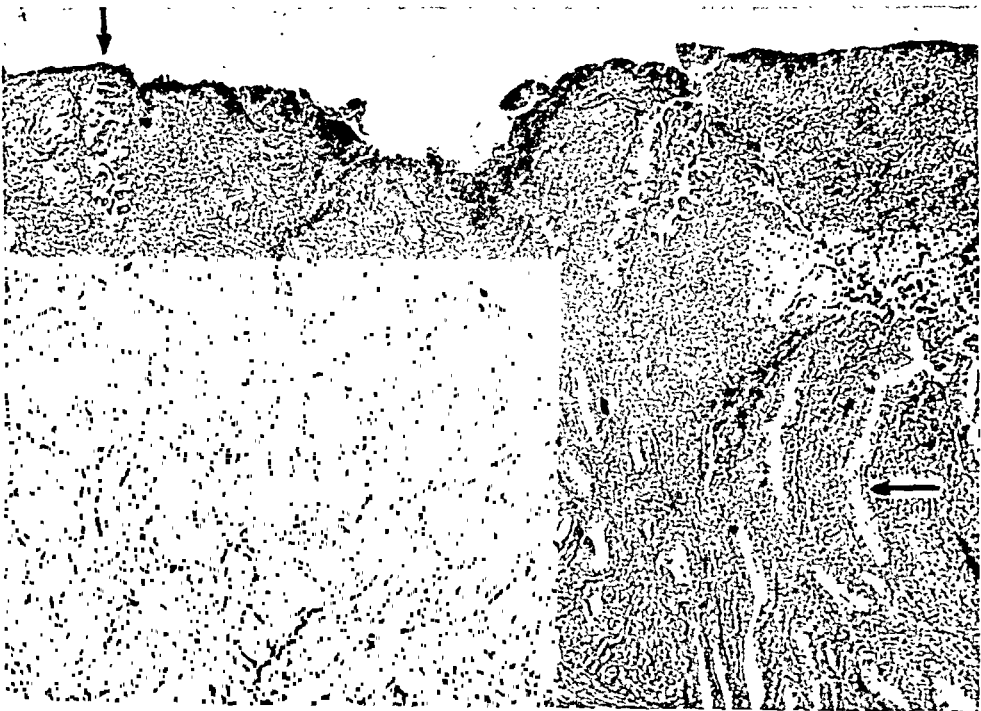


Fig. 11.

Patient 59 had a seven-month period of amenorrhea following x-ray therapy. The menstrual flow at the time of operation was scant. The endometrium had sloughed in portions and in others was low and atrophic. There was no sign of previous stimulation by the corpus luteum hormone.

TABLE I. NORMAL MENSTRUATION

PATIENT	AGE	CONCOMITANT PELVIC PATHOLOGY	FUNCTIONING CORPUS LUTEUM	ENDOMETRIUM	DAY OF CYCLE OPERATED.
<i>Normal Menstruation</i>					
1	45	Residues	None	Resting	8
2	45	Adenomyosis	None	Proliferative	9
3	36	Residues	None	Proliferative	10
4	39	None	None	Proliferative	11
5	32	None	None	Proliferative	12
6	36	Residues	None	Proliferative	13
7	35	Residues	None	Proliferative	14
8	44	Uterine prolapse	None	Proliferative	1
9	37	Endometriosis	Young	Progravid	14
10	33	Endometriosis	Vascularization	Progravid	16
11	30	None	Young	Progravid	16
12	37	None	Vascularization	Progravid	17
13	46	Endometriosis	Vascularization	Progravid	18
14	46	Ovarian tumor	Bloom	Progravid	19
15	40	None	Bloom	Progravid	21
16	42	Endometriosis	Bloom	Progravid	21
17	45	None	Bloom	Progravid	22
18	29	Endometriosis	Regression	Menstruating	25
19	35	Ovarian tumors	Bloom	Progravid	26
20	46	None	Bloom	Progravid	27
21	29	None	Bloom	Progravid	28
22	46	Residues	Beginning Regression	Progravid Involution	30
<i>Slight Menorrhagia</i>					
23	26	Perisalpingitis	None	Menstruating	1
24	36	None	None	Menstruating	2
25	46	None	None	Menstruating	2
26	45	Residues	None	Menstruating	4
27	42	Residues	None	Resting	10
28	39	Residues	None	Proliferating	12
29	36	None	None	Proliferating	12
30	47	Endometriosis	None	Proliferating	12
31	45	None	None	Proliferating	14
32	36	None	Young	Progravid	16
33	49	Endometrial polyp	Bloom	Progravid	16
34	36	Residues	Bloom	Progravid	18
35	45	Residues	Vascularization	Progravid	25
36	37	None	Bloom	Progravid	23
37	40	Residues	Bloom	Progravid	32
<i>Menorrhagia</i>					
38	36	Residues	None	Menstruating	3
39	44	Endometriosis	None	Resting	6
40	39	None	None	Proliferating	8
41	38	None	None	Proliferating	16
42	37	Residues	None	Proliferating	16
43	49	Residues	None	Proliferating	32
44	41	Endometriosis	Vascularization	Progravid	17
45	35	Residues	Bloom	Progravid Involution	29
46	35	Previous operation Residues	Bloom	Progravid	29
47	40	Parovarian cyst 2 cm.	Bloom	Progravid Involution	29
48	39	Residues	None	Proliferative	?

of the endometrium in the process of desquamation is shown in Fig. 12. Adjacent to this, the endometrium was pro gravid in character, but it was not completely normal. Stimulation by the corpus luteum hormone is present, however. In other regions the endometrium is much thicker and is in the proliferative phase without signs of corpus luteum hormonal stimulation (Fig. 13). In the ovary, there is a histologically normal corpus luteum in the stage of bloom (Fig. 14). The explanation of such findings is not immediately apparent. It may be that our criteria for



Fig. 13.



Fig. 14.

the diagnosis of a normal corpus luteum by histologic methods are inadequate. More logically, however, the explanation is to be found in the fact that the corpus luteum is normal and that the bleeding endometrium is incapable of responding in a normal manner.

In Patients 90 and 91, who had been bleeding continuously for some time (Fig. 5, B), the corpora lutea were normal and the endometria were pro gravid. The

TABLE I—CONT'D

PATIENT	AGE	CONCOMITANT PELVIC PATHOLOGY	FUNCTIONING CORPUS LUTEUM	ENDOMETRIUM	DAY OF CYCLE OPERATED
<i>Oligomenorrhea</i>					
92	37	Residues	None	Proliferative	18
<i>Amenorrhea</i>					
93	37	Residues	None	Proliferative	12
94	41	None	Vascularization	Progravid	39
95	52	Endometriosis	None	Proliferative	47
96	51	Pyometria	None	Resting	11 yr.
<i>Pregnancy</i>					
97	28	None	Pregnancy	Decidua	1 mo.
98	33	Placenta previa	Pregnancy	Decidua	5 mo.
99	36	None	Pregnancy	Decidua	6 mo.
100	39	Chorioepithelioma	None	Proliferative	3 mo.

endometriums had responded to the stimulation received from the respective corpora lutea. Ovulation had occurred and corpus luteum development had progressed normally in these individuals during a prolonged phase of active endometrial bleeding. The findings in Patient 89 were similar to the two just described, except that the corpus luteum was cystic (Table I). The individual cells appeared normal. The endometrium evidenced gravid changes which indicated that the corpus luteum had exerted its influence in spite of its cystic condition. Ovulation undoubtedly had occurred during the active bleeding phase of six weeks' duration.

No endometrial cystic glandular hyperplasia was present in these patients who possessed corpora lutea and who complained of abnormal uterine bleeding.

One patient (Patient 92, Table I) complained of an oligomenorrhea. The endometrium was proliferative, and there was no corpus luteum in the ovaries when the tissues were removed on the eighteenth day.

Four patients complained of amenorrhea (Patients 93, 94, 95, and 96, Table I). One was in the menopause (Patient 95) and another was eleven years postmenopausal (Patient 96). Patient 94 was operated upon on the thirty-ninth day of the cycle. At this time the menstrual period was thirteen days overdue. She had never missed a period before. A normal corpus luteum in the vascularization stage was present in the ovary. The endometrium was early gravid. These findings would be expected about the thirteenth day of this patient's usual twenty-six-day cycle. The evidence indicates that a complete cycle had passed without a bleeding phase and that ovulation of the next cycle had occurred in a perfectly rhythmic manner. Markee (1940) has observed similar cyclic manifestations of ovulation in the monkey (*Macacus rhesus*).

Three patients (Patients 97, 98, and 99) were pregnant when the uterus was removed (Table I). The endometriums had the normal decidua, glands, and vascular development of pregnancy. The corpora lutea were normal.

One patient (Patient 100, Table I) had a chorioepithelioma and had been bleeding continuously for three months. No corpus luteum was demonstrable in either ovary. The endometrium was proliferative in type.

SUMMARY

Ovulation had occurred in these 100 unselected and consecutively operated patients in a manner similar to that observed in normal women. Forty-six patients had functioning corpora lutea of the present cycle. Not counted in the 46 patients were many patients who are listed as not having corpora lutea of the present cycle but who had corpora lutea of the previous cycle in the regression phase. Their presence suggests that ovulation, corpus luteum development, and the

TABLE I—CONT'D

PATIENT	AGE	CONCOMITANT PELVIC PATHOLOGY	FUNCTIONING CORPUS LUTEUM	ENDOMETRIUM	DAY OF CYCLE OPERATED
<i>Metrorrhagia</i>					
49	41	None	None	Proliferative	10
50	35	Residues	None	Proliferative	13
51	52	None	None	Menstruating	27
				Progravid	2
52	35	Residues	None	Menstruating	31
				Progravid	2
53	50	None	None	Proliferative	42
54	36	None	Bloom	Progravid	16
55	46	Endometriosis	Vascularization	Progravid	17
56	42	None	Bloom	Progravid	25
<i>Menorrhagia and Metrorrhagia</i>					
57	36	Residues	None	Menstruating	4
58	34	Residues	None	Menstruating	4
59	38	Residues	None	Menstruating	7
				Atrophic	
60	40	Endometriosis	None	Menstruating	8
		Residues			
61	36	Endometriosis	None	Resting	9
62	45	Residues	None	Proliferative	10
63	47	Adenomyosis	None	Proliferative	10
64	38	None	None	Menstruating	11
				Proliferative	
65	33	None	None	Proliferative	13
66	38	Residues	None	Resting	19
67	45	None	None	Resting	19
68	38	Parovarian cyst 12 cm.	None	Resting	21
69	40	None	None	Resting	23
70	39	Residues	None	Menstruating	36
71	45	None	None	Resting	38
72	44	None	None	Proliferative	40
				Polypoid	
73	46	None	None	Proliferative	48
				Sl. hyperplasia	
74	43	None	None	Menstruating	50
75	47	Endometriosis	None	Menstruating	50
				Resting	
76	31	None	Vascularization	Progravid	9
77	47	None	Bloom	Progravid	12
78	36	None	Regression	Menstruating	14
			Bloom	Progravid	
79	37	Residues	Bloom	Progravid	15
80	40	Residues	Vascularization	Progravid	16
81	46	Residues	Vascularization	Progravid	17
82	43	Residues	Bloom	Progravid	23
83	34	Residues	Bloom	Progravid	23
84	39	None	Bloom	Progravid	23
85	40	Residues	Bloom	Beginning	27
				Menstruation	
86	47	Endometriosis	Vascularization	Progravid	?
87	44	Residues	Bloom	Menstruating	45
				Progravid	
				Proliferative	
88	47	Endometriosis	Bloom	Progravid	18
89	46	Residues	Bloom	Progravid	52
90	43	None	Bloom	Progravid	70
91	36	None	Bloom	Progravid	120

CONCLUSIONS

All of the above facts obtained from a critical study of these 100 patients with uterine fibroids indicate that the ovarian and endometrial relationships were not significantly altered in the cycles observed. There was no evidence of excessive or unopposed estrogenic stimulation.

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104 SOUTH MICHIGAN BOULEVARD

DISCUSSION

DR. GEORGE H. GARDNER.—No one doubts that women with fibroids ovulate normally at times, but it is amazing that "functioning" corpora lutea were found in 47 per cent of this unselected series. Uterine fibroids are at times accompanied by enlarged, gray, edematous, cystic ovaries. Consequently, it is disconcerting that these so-called "oyster ovaries" were almost absent from the Brewer-Jones series. Two of their other observations are strong evidence against the improbable thesis that uterine fibroids result from prolonged, excessive, estrogenic hormone stimulation, for hyperplasia of the endometrium was encountered only once, and corpora lutea with corresponding secretory response by the endometria were frequent, not exceptional, findings.

Certain "misfit" cases, i.e., those in which the response of the endometrium did not coincide with the appearance of the corpus luteum, have been presented. I believe that the authors are justified in using this term and in presuming to estimate corpus luteum function, from the histologic appearance of lutein cells.

These cases conclusively demonstrate that functional uterine bleeding may arise from secretory endometrium and that bleeding is not invariably anovulatory. Some of the misfits are striking examples, both of irregular ripening and irregular shedding of the endometrium. Such observations are additional proof that the uterine mucosa does not always follow the rule of "all or none" response to hormone stimulation. Local mechanical interference by the uterine fibroids suggests itself as an explanation for the presence of some "misfit" cases. Tumors may compress, distort and so interfere with the blood supply of the ovaries that their function is seriously altered; as a result both follicles and corpora lutea may mature slowly and unequally; by the same token, the corpora lutea may involute in an unusual manner. In consequence the progesterone stimulation of the endometrium may lack rhythm, be protracted, and even be modified by the developing follicle of an oncoming cycle. Furthermore, the structure of the endometrium may be so disturbed by fibroids, especially those which encroach on the uterine cavity, that it cannot respond in its usual

endometrial response had occurred normally in the preceding cycle. The findings indicate that ovulation takes place most frequently about the midpoint of the menstrual cycle as in normal women. In one instance, ovulation occurred on or about the sixth day (Patient 76). Ovulation occurred early in the cycle also in Patient 77. Ovulation occurred after a period of amenorrhea in one patient (Patient 94). This is identical to the phenomenon as it is observed in normal women without fibroids. Four of these 100 patients were pregnant or had a complication of pregnancy at the time of operation. This indicates positively that ovarian function can be normal in women with fibroids.

There were two corpora lutea with identical development in the ovaries of each of 4 patients. In another patient, there were two corpora lutea in one ovary and one in the other ovary, all having the same degree of development. Multiple ovulation occurs in normal women in approximately the same number of instances as found in these 100 patients.

Ovulation in three instances occurred during a prolonged phase of active uterine bleeding (Patients 87, 89, and 90).

In the 37 patients with normal menstrual cycles (Figs. 1 and 2), ovulation had failed to occur by the fifteenth day in but one patient. This patient (Patient 8) demonstrated, in all probability, an instance of cyclic anovulatory menstruation which is not strictly an abnormal phenomenon.

In all the patients complaining of abnormal uterine bleeding (Figs. 3, 4, and 5), ovulation had not occurred by the fifteenth day in 14 patients but had occurred in 21 patients.

Four additional patients were menopausal or postmenopausal. In these ovulation, as would be expected, had not occurred.

If 100 normal women were operated upon consecutively without consideration of the stage of the cycle, it is doubtful if ovulation would be found with any greater frequency than was observed in the patients studied in this report.

The development of the corpora lutea was normal in 41 of the 46 patients. Evidence that the development was normal was obtained by histologic study of the corpora lutea and by the histologic study of the endometriums which reflected the characteristic responses to normal corpus luteum hormonal stimulation. In those patients with abnormal uterine bleeding, the normal relationship between the corpus luteum and the endometrium was maintained in most instances.

Small follicular cysts were present in 21 of the 100 patients. In no instance was there evidence that these cysts had had any influence on the normal physiologic processes of the ovaries or the endometriums. Normal functioning corpora lutea were present in the ovaries of 5 of these patients. Hyperplasia or excessive estrogen stimulation of the endometrium was present in none.

So-called cystic glandular hyperplasia was present in a moderate degree in only one instance in the entire group of 100 patients with fibroids. This finding is at marked variance with the generally accepted clinical impression.

Henceforth, follow-up studies will be more comparable among themselves, and many cases from different clinics can be "pooled" in the literature. We are indebted to the American Committee on Maternal Welfare for a uniform terminology and set of criteria for the classification of the toxemias.

In the present paper we shall report the findings at follow-up in a large series of nonconvulsive toxemias classified by the new system. Vomiting of pregnancy has been excluded. An analysis of factors associated with later hypertension will be presented.

MATERIAL AND METHODS

In 1935 and 1936 the 10,627 deliveries in the Margaret Hague Maternity Hospital included 645 cases of late nonconvulsive toxemia, an incidence of 6.07 per cent. In 1940 we have re-examined 466, or 72 per cent, of these toxemias.

Blood pressure readings were made with a mercury sphygmomanometer, with the patient lying down. After a rest period of five minutes, and quiet reassurance, the pressure was checked. The lower reading is reported. The diastolic pressure was taken as the point at which the sounds suddenly became muffled and dull. The eye grounds were examined without mydriasis. The cardiac size was estimated by palpation of the point of maximal impulse; when this was not felt, 6 foot x-ray plates were taken. When the specific gravity of the morning urine was less than 1.022, blood chemistries and urea clearances were done.

Urinary protein was determined by the sulfosalicylic acid method. Blood and urine ureas were measured by Van Slyke's⁶ manometric procedures. Usually the urine output permitted the calculation of maximal clearances; voided urines were used, and the patients were ambulatory.

The new toxemia classification adopted by the American Committee on Maternal Welfare⁷ was used to classify the patients upon the basis of the information available at the time of the toxic pregnancy of 1935 or 1936, and without regard for the status at follow-up. When the toxic manifestations (hypertension, proteinuria, edema) were definitely known to have first appeared later than the twenty-fourth week of pregnancy, the toxemia was called *pre-eclampsia*. Mild and severe pre-eclampsia were divided on the basis of blood pressure below or above 160/110,

TABLE I. DISTRIBUTION OF THE TOXEMIAS RE-EXAMINED IN 1940

All patients had toxemia in 1935 or 1936. "Hypertension" refers to any blood pressure greater than 140/90. All percentages based upon numbers of patients seen in 1940.

GROUP	NUMBER OF CASES	IMMEDIATE DEATHS	REMOTE DEATHS	FETAL MORTALITY PER CENT	FOLLOW-UP FINDINGS				PREGNANT AGAIN	RECURRENCE OF TOXEMIA PER CENT
					HYPERTENSION PER CENT		PROTEINURIA PER CENT			
Mild pre-eclampsia	267	0	5	7.12	37.45	(32.60) *	21.0	(2.3) †	134	32.8
Severe pre-eclampsia	52	3	1	38.50	42.32	(36.55)	17.3	(1.9)	21	66.7
Renal disease	14	0	4	57.14	78.60	(78.60)	78.6	(78.6)	0	
Hypertension	41	0	3	34.15	100.00	(100.0)	41.5	(2.4)	9	88.9
Hypertension (?)	41	0	2	29.27	87.80	(87.80)	28.2	(2.6)	19	73.7
Unclassified	51	0	1	27.45	72.58	(51.00)	33.3	(10.0)	20	65.0
Total	466	3	16	19.85	53.08	(47.22)	26.2	(5.5)	203	45.8

*Figures in parentheses exclude patients with either systolic or diastolic elevation alone.

†Figures in parentheses exclude patients showing only a "very faint trace" of protein by sulfosalicylic acid method.

manner even to normal hormone stimulation. Spiral arteries may be inadequate or abortive; this might lead to premature focal ischemia of the mucosa and result in abnormal uterine bleeding.

DR. RALPH A. REIS.—When someone as capable as Dr. Brewer denies his ability to handle more than 100 cases it takes courage to speak on 1,000. We analyzed 1,000 cases at Michael Reese Hospital. First, we found no relation between the state of the endometrium and the state of the cyclic development of the corpus luteum and other changes. Second, the bleeding that occurred as we found it was either on a mechanical basis due to submucous fibroids or from pressure atrophy of the endometrium, or from a rather frequent association of adenomyosis and fibroids. It is our impression that in many of our patients the bleeding is not due to intramural or submucous fibroids but to adenomyosis and fibroids. In our 1,000 cases there were about 25 per cent that showed ovarian pathology. I think that refutes Witherspoon's theory that chronic inflammation sets up a cycle that eventuates fibroids.

I would like to ask Dr. Brewer whether in these 100 patients adenomyosis of the uterine wall was found to any extent.

DR. BREWER (closing).—In answer to Dr. Reis' question, there were not more than five that had adenomyosis associated with fibroids. There were many more patients with endometriosis.

AN ANALYSIS OF SOME FACTORS ASSOCIATED WITH POSTTOXEMIC HYPERTENSION

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AS EARLY as 1851, Frerichs¹ thought that eclampsia might cause a subsequent "chronic nephritis." The earlier literature, summarized by Koblanck² (1894), was based chiefly upon autopsy findings, or upon the detection of proteinuria at follow-up. Later studies have included blood pressure measurements, and the demonstration of hypertension at follow-up has been taken as evidence for chronic nephritis, even long after the establishment of the conception of vascular hypertension. After reviewing the literature most capably, Bell³ (1932) concluded that a mild degree of change in the renal blood vessels may often persist after toxemia of pregnancy. He believes that the later hypertension found by so many writers may be caused by the persistence of the glomerular capillary changes which he had found in his own material. Other recent reviews of the literature of posttoxemic hypertension have been given by Siedentopf and Major⁴ (1936) and Browne and Dodds⁵ (1939).

The estimated frequency of hypertension in such follow-up studies ranges from less than 2 per cent to over 60 per cent. The average incidence of hypertension after toxemia of pregnancy would seem to be about 45 per cent, to judge from the literature.

California. The third is that of Saller¹¹ from the Kiel outpatient clinic; of these, 1,142 are in the same age groups as our patients. The age groups of these control series were weighted so as to correspond with the age distribution in our post-toxemic women, and the data of the 3 series were combined. The corrected frequency curves were then drawn in Fig. 1, which also compares the blood pressures found in our posttoxemic patients.

As one compares the control curves with those for the posttoxemic women, it is evident that there is a greater incidence of hypertension in the posttoxemics, whatever blood pressure level one may choose as the dividing line between normal and hypertensive states.

Proteinuria.—In 73.8 per cent of all patients, no protein was detected in the voided urine at follow-up. In the great majority of the rest, the proteinuria was only a "very faint trace" by the sulfosalicylic acid method. Short and Ley¹² have recently demonstrated as much protein in the urines of 20 to 30 per cent of nearly 5,000 women life insurance policy holders. In 5.5 per cent of all our cases, the proteinuria was present in possibly significant degree. Most of these patients were in the renal disease or unclassified groups. Table I presents the results for each category of toxemia.

Blood Chemistry.—The only blood chemical findings of any significance were in the renal disease group, and in 12 patients who now have recognizable diabetes. In 10 of these diabetics, the hyperglycemia has appeared since the toxic pregnancy of 1935 or 1936.

Urea Clearance.—Urea clearances were not done in 229 of the cases, since the urinary specific gravity exceeded 1.022 in the absence of proteinuria and sugar, and

TABLE II. RENAL FUNCTION AT FOLLOW-UP

	URINARY SPECIFIC GRAVITY MORE THAN 1.022	URINARY SPECIFIC GRAVITY LESS THAN 1.022				
		NORMAL BLOOD PRESSURE		HYPERTENSION		TOTAL WITH RENAL IMPAIR- MENT PER CENT
		UREA CLEARANCE LESS THAN 60 PER CENT	UREA CLEARANCE MORE THAN 60 PER CENT	UREA CLEARANCE LESS THAN 60 PER CENT	UREA CLEARANCE MORE THAN 60 PER CENT	
Mild pre-eclampsia	161	1	56	5	44	2.25
Severe pre-eclampsia	19	1	15	3	14	7.69
Renal disease	0	2	0	10	2	85.70
Hypertension	12	0	0	2	27	4.88
Hypertension (?)	14	0	1	3	23	7.32
Unclassified	23	3	3	2	20	9.81
Total	229	7	75	25	130	6.87

TABLE III. ANATOMIC FINDINGS IN PATIENTS HYPERTENSIVE AT FOLLOW-UP

GROUP	EYE GROUND CHANGES			CARDIAC ENLARGEMENT			RADIAL ARTERY SCLEROSIS CASES
	CASES	PER CENT OF ALL CASES	PER CENT OF HYPER- TENSIVES	CASES	PER CENT OF ALL CASES	PER CENT OF HYPER- TENSIVES	
Mild pre-eclampsia	30	11.36	30.30	29	10.97	29.30	0
Severe pre-eclampsia	11	21.15	50.00	9	17.32	40.90	1
Renal disease	8	57.20	72.70	8	57.20	72.70	0
Hypertension	23	56.10	56.10	26	63.40	63.40	7
Hypertension (?)	21	51.20	58.35	21	51.20	58.35	2
Unclassified	16	31.38	43.25	12	23.53	32.42	2
Total	109	23.45	44.30	105	22.58	42.68	12

proteinuria less or more than 6 Gm. per liter, edema slight or marked, the absence or presence of symptoms, and the response to treatment. When known hypertension antedated the pregnancy, or appeared before the twenty-fourth week, it was considered that the patient had either *hypertensive* or *renal disease*. These were differentiated on the basis of history, degree of proteinuria, type of urinary sediment, and renal function tests. The *unclassified toxemias* are those in which the data were incomplete. As a subgroup of the *unclassified* category we have separated patients thought to belong with the hypertensives, because of the absence of all signs and symptoms other than a blood pressure greater than 180/100. However, their status before the twenty-fourth week of pregnancy was unknown, so we have called them "*hypertension (?)*." Since 88 per cent of these had hypertension at follow-up, it seems that this criterion has some value. The distribution of the different groups is set forth in Table I. Only those patients seen in 1940 are included in any of the tables and analyses to be presented.

Our standard for hypertension is any pressure greater than 140 mm. Hg in the systolic or 90 mm. Hg in the diastolic readings.

REMOTE MATERNAL MORTALITY

Of the 642 survivors discharged from the hospital, 16, or 2.96 per cent, are known to have died; 12 of these deaths were in the cardiovascular field, 4 being associated with toxemia in the subsequent pregnancy. Table I shows the distribution of these remote deaths in relation to the toxemia classification.

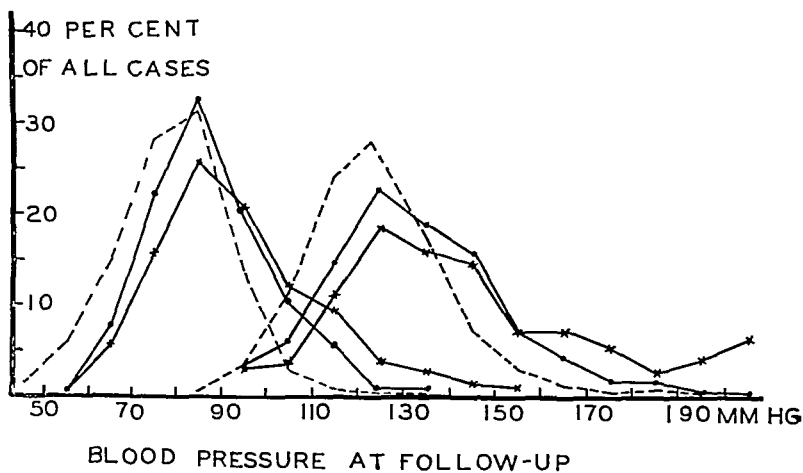


Fig. 1.—The frequency distributions of diastolic and systolic blood pressures at follow-up in 1940, as compared with control series described in text. Control series from publications of Alvarez and Zimmermann, Wetherby, and Saller. Patients who had mild pre-eclampsia in 1935 or 1936. All patients having nonconvulsive toxemia in 1935 or 1936. Controls, -----; mild pre-eclampsia, - . - . ; all cases, x—x—x.

FINDINGS AT FOLLOW-UP

Hypertension.—Table I shows that very nearly half (47.2 per cent) of all non-convulsive patients re-examined now have hypertension at $3\frac{1}{2}$ to $5\frac{1}{2}$ years after the toxemia of 1935 or 1936. A few patients have an elevation in either the systolic or the diastolic pressure, but not in both. If these be considered as hypertensive, then the incidence of hypertension becomes 53.08 per cent. In Fig. 1 are plotted the frequency distributions of the systolic and diastolic pressures as found at follow-up.

We have used, as a control series, the published data of 3 writers who have described the range of blood pressure in women. Wetherby⁹ reports the pressures in women attending the outpatient clinic in Minneapolis. Of this series, 1,544 cases are in the age groups represented by our patients. A second series is that of Alvarez and Zimmermann¹⁰ for 216 unmarried women from the office practice of Alvarez in

Initial Blood Pressure Reading.—The lower the first observed systolic blood pressure, one month or more before delivery, the less likely toxemia is to recur, or hypertension is to be found at follow-up. This is true especially in the normal, and even the low normal range of blood pressure. Taking only the pre-eclamptic patients (though the same observation is valid for all cases), we find the conditions as indicated in Table V.

The first observed systolic pressure is often higher than subsequent readings, before the onset of toxemia. Perhaps the patients with the higher initial pressures have reacted more to the emotional stimulus of the first clinic visit. This interesting correlation between the first observed blood pressure and subsequent hypertension might be compared with the predictive value of the cold pressor test for hypertension as alleged by Hines and Brown.¹⁴ Robinson and Brucer¹⁵ examined a large number of life insurance policy holders at yearly intervals, and found that "... men with moderately high systolic pressures (120 to 140 mm.) at any age, but especially in the younger groups, are probably the ones who will have hypertension years later."

Time of Onset and Duration of Toxemia.—Since patients having an early onset of toxemia are liable to be carried for prolonged periods, to improve the chance of fetal survival when delivered, the time of onset and duration of toxemia will be considered together. In addition, however, we shall attempt to separate these factors in their influence upon permanent hypertension and upon the recurrence of toxemia.

Onset of toxemia before the thirty-eighth week is associated with a greater probability of toxemia recurrence and of hypertension at follow-up, though there is apparently no direct relation between time of onset and these sequelae (Table VI).

TABLE VI. THE INCIDENCE OF LATER HYPERTENSION AND RECURRENCE OF TOXEMIA AS INFLUENCED BY TIME OF ONSET OF TOXEMIA

ONSET OF TOXEMIA	BEFORE SEVENTH MONTH	SEVENTH TO EIGHTH MONTH	EIGHTH TO EIGHT AND ONE-HALF MONTH	EIGHT AND ONE-HALF TO NINTH MONTH	POST-MATURELY
Incidence of hypertension at follow-up	62.5%	40.0%	53.2%	15.8%	26.5%
Recurrence of toxemia	75.0%	42.8%	46.7%	26.8%	40.0%

TABLE VII. THE PARALLELISM OF DURATION OF TOXEMIA WITH THE INCIDENCE OF HYPERTENSION AT FOLLOW-UP AND WITH RECURRENCE OF TOXEMIA

DURATION OF TOXEMIA	0 TO 1 WEEK	1 TO 2 WEEKS	2 TO 3 WEEKS	3 TO 4 WEEKS	4 TO 6 WEEKS	MORE THAN 6 WEEKS
Incidence of hypertension at follow-up	13.7%	40.0%	48.6%	71.1%	66.7%	71.4%
Recurrence of toxemia	24.4%	29.0%	37.5%	72.2%	66.7%	100.0%

Considering the duration of toxemia without regard for the time of onset, we find the incidence of hypertension and recurrence of toxemia as shown in Table VII.

It appears that the duration of toxemia has a more nearly proportional effect upon subsequent hypertension and recurrence of toxemia than has the time of onset. In Fig. 2 we have plotted the data for mild and severe pre-eclampsics plus 97 eclampsics. Duration of toxemia parallels the incidence of later hypertension in all of these groups. However, these data have not been controlled with respect to time of onset of toxemia. Such an analysis is presented in Table VIII, which indicates strongly that time of onset of toxemia, per se, has no effect upon the appearance of hyperpiesia at follow-up. *The controlling factor is duration of toxemia.* This is true in women who have had no other toxemic pregnancy, as well as in women with history of an earlier or later toxemia. The recurrence of toxemia

it was thought that the clearances would be normal (Chesley¹³). Of the remaining 237, only 32 had urea clearances below 60 per cent (taken as the lower limit of normal). Twelve of these were in the renal disease group. At most, then, only 6.9 per cent of the posttoxemics show renal impairment. Excluding the cases of renal disease, only 4.3 per cent have demonstrably impaired kidney function. The results for the different groups are summarized in Table II.

Physical Findings.—Of the 246 patients found to have hypertension at follow-up, 109 (44.3 per cent) had eye ground changes, and 105 (42.7 per cent) had cardiac enlargement. In addition to these hypertensives, 6 women with normal blood pressures show eye ground changes, and 1 has cardiac enlargement (rheumatic heart disease). The results of the physical examinations are detailed in Table III.

FACTORS AFFECTING THE PERSISTENCE OF HYPERTENSION AND THE RECURRENCE OF TOXEMIA

In the analysis of factors affecting the persistence of hypertension, the pre-eclamptic group patients (319) provide the data unless otherwise specified. For recurrence of toxemia, the data are for the 145 pre-eclamptic patients having subsequent pregnancies.

In general, the same factors affect the recurrence of toxemia as affect the persistence of hypertension. While many of these factors are of purely academic interest when considered in relation to permanent hypertension alone, they have a very definite practical value in their relation to the recurrence of toxemia. As will be demonstrated, another toxic pregnancy, after a first toxemia, increases the chances of later hypertension. If one can judge the probabilities of recurrence of toxemia, perhaps some degree of control over the later appearance of hypertension may be expected.

Family History.—We do not consider that the family histories possess any high degree of reliability, but nevertheless there does appear to be a correlation between hypertension at follow-up and the patients' stories of high blood pressure, "heart trouble" (nature unspecified), kidney trouble, strokes, and diabetes in near relatives. We have combined these various manifestations of possible cardiovascular disease; whenever such a positive history was elicited in the pre-eclamptic groups, the chances for hypertension were increased. The effect upon the recurrence rate for toxemia is slight (Table IV).

TABLE IV.—THE EFFECT OF FAMILY HISTORY OF CARDIOVASCULAR DISEASE IN ENHANCING THE PROBABILITY OF HYPERTENSION AND RECURRENCE OF TOXEMIA

	FAMILY HISTORY NEGATIVE	FAMILY HISTORY POSITIVE
Incidence of hypertension at follow-up	21.2%	36.1%
Recurrence rate of toxemia	37.7%	48.1%

TABLE V. THE RELATION BETWEEN THE FIRST OBSERVED SYSTOLIC BLOOD PRESSURE, BEFORE ONSET OF TOXEMIA, AND THE INCIDENCE OF LATER HYPERTENSION AND RECURRENCE OF TOXEMIA

INITIAL BLOOD PRESSURE	LESS THAN 100	101-110	111-120	121-130	131-140	141 PLUS
Incidence of hyperten- sion at follow-up	7.69%	20.51%	35.90%	55.20%	43.23%	46.67%
Recurrence of toxemia	0.0 %	20.0 %	40.6 %	51.5 %	41.7 %	42.1 %

also seems to depend upon the duration of the original toxemia. The data in Table VIII include the 97 eclamptic cases, added to augment the numbers of cases in each subdivision.

Height of Blood Pressure and Degree of Proteinuria in Toxemia.—The more severe the degree of hypertension during the toxic pregnancy, the greater the incidence of later hypertension and of toxemia recurrence. The same unfavorable prognosis holds when proteinuria increases concomitantly with hypertension. But this is not the most significant feature of the proteinuria. For at a given level of hypertension, the greater the proteinuria, the better the patient's chance of escaping hypertension at follow-up. Abundant proteinuria seems usually to augur well for the patient's future, as has been pointed out by Berman.¹⁶ The data for pre-eclamptic patients are shown in Table IX.

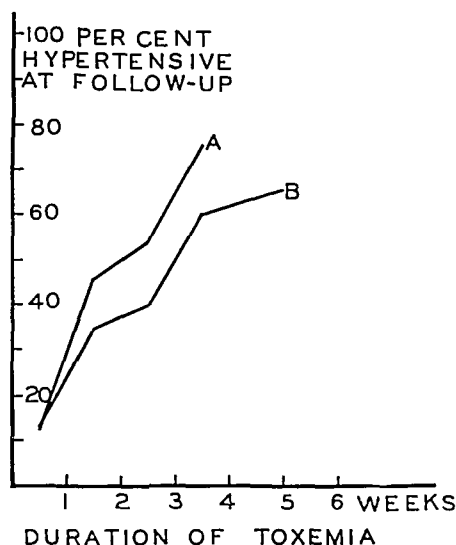


Fig. 2.—The relation between duration of toxemia in pregnancy and the incidence of hypertension at follow-up in 1940. *A*, Patients who had mild pre-eclampsia in 1935 or 1936. *B*, Patients who had mild or severe pre-eclampsia in 1935 or 1936, together with all cases of eclampsia from 1931 to 1940.

Findings at Ten Days and Six Weeks Post Partum.—So far as the pre-eclamptics are concerned, neither the blood pressure nor the proteinuria at ten days has any significance in predicting subsequent hypertension. There is a marked relation between these findings and the recurrence of toxemia, which is nearly doubled in those patients whose toxic signs persist for ten days post partum. The blood pressure at six weeks post partum is a valuable indication as to the probability of toxemia recurrence or later hypertension, though it is not reliable by itself. In the summary in Table X, "elevated blood pressure" refers to any tension of 140/90 or greater.

Age at Follow-Up.—The older the patient at follow-up, the more likely hypertension is to be found. This is to be expected from the fact that the incidence of

TABLE IX. THE INCREASING INCIDENCE OF LATER HYPERTENSION AND RECURRENCE OF TOXEMIA IN RELATION TO INCREASING SEVERITY OF TOXEMIA

BLOOD PRESSURE AVERAGE, MM. HG	LESS THAN 140		141 TO 180		181 TO 220		MORE THAN 221	
	LESS	MORE	LESS	MORE	LESS	MORE	LESS	MORE
PROTEINURIA, MORE OR LESS THAN 3 g/L								
Incidence of hypertension at follow-up	37.5%	0.0	44.3%	21.0%	80.0%	53.8%	—	100%
Recurrence of toxemia	33.3%	0.0	41.5%	28.0%	—	66.7%		

TABLE VIII. THE EFFECT OF DURATION OF TOXEMIA, INDEPENDENTLY OF TIME OF ONSET, UPON THE INCIDENCE OF SUBSEQUENT HYPERTENSION, AND RECURRENCE OF TOXEMIA. DATA FOR MILD AND SEVERE PRE-ECLAMPTICS COMBINED

ONSET OF TOXEMIA	BEFORE SEVENTH MONTH				SEVENTH TO EIGHTH MONTH				EIGHTH TO NINTH MONTH				POSTMATURE			
	MORE THAN 3 WEEKS		LESS THAN 3 WEEKS		MORE THAN 3 WEEKS		LESS THAN 3 WEEKS		MORE THAN 3 WEEKS		LESS THAN 3 WEEKS		MORE THAN 3 WEEKS		LESS THAN 3 WEEKS	
CARRIED WITH TOXEMIA	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION	CASES	PER CENT HYPERTENSION
Primiparas, and multiparas with no history of toxemia	6	66.7	4	0.0	5	60.0	10	10.0	19	63.2	85	15.3	1	100.0	20	15.0
Multiparas with history of toxemia, or history unknown	1	100.0	2	0.0	13	61.6	7	28.6	28	82.2	29	24.1	1	100.0	12	33.3
Eclampsia (series in preparation)	11	63.6	7	28.6	5	80.0	10	20.0	8	25.0	58	15.5	0	—	2	0.0
Total	18	66.7	13	15.4	23	65.3	27	18.5	55	67.2	172	16.8	2	100.0	34	20.6
Recurrence of toxemia in later pregnancies	5	60.0	6	33.3	10	70.0	20	35.0	24	62.5	97	33.3	1	100.0	27	25.9

TABLE XIII. THE NATURE OF SUBSEQUENT PREGNANCIES AND THE INCIDENCE OF LATER HYPERTENSION

SUBSEQUENT PREGNANCY	NONE	ONE		TWO		
		TOXIC	NORMAL	BOTH TOXIC	ONE TOXIC ONE NORMAL	BOTH NORMAL
Incidence of hypertension	44.7%	64.6%	11.7%	80.0%	50.0%	8.3%

TABLE XIV. THE INCIDENCE OF HYPERTENSION AS CORRELATED WITH THE NATURE OF ALL PREGNANCIES OTHER THAN THE TOXIC ONE OF 1935 OR 1936

ALL OTHER PREGNANCIES	NONE	ALL NORMAL	TOXEMIA IN AT LEAST 1 OTHER	HISTORY OF TOXEMIA UNCERTAIN
Incidence of hypertension at follow-up	31.5%	8.5%	61.9%	58.1%

The interval from delivery, in the toxic pregnancy, to the subsequent conception bears no definite relation to the incidence of later hypertension, or to the recurrence rate of toxemia (Table XV).

TABLE XV. THE INTERVAL FROM TOXEMIA TO SUBSEQUENT CONCEPTION IN ITS BEARING UPON THE INCIDENCE OF LATER HYPERTENSION AND THE RECURRENCE OF TOXEMIA

DELIVERY TO CONCEPTION	LESS THAN 3 MONTHS	3 TO 6 MONTHS	7 TO 12 MONTHS	13 TO 24 MONTHS	25 TO 36 MONTHS	MORE THAN 37 MONTHS
Incidence of hypertension at follow-up	33.3%	38.5%	39.2%	25.7%	38.1%	45.5%
Recurrence of toxemia	33.3%	35.7%	36.4%	34.2%	42.9%	54.6%

Ante-partum Care.—The recurrence rate of toxemia in later pregnancies was not reduced by the medical care given in these later pregnancies. The number of patients receiving no care is too few to form an accurate opinion, but it appears that the recurrence rate of toxemia was increased in those pre-eclamptic patients who placed themselves under medical supervision before delivery.

These data, while discouraging, in no way negate the desirability of prenatal care, in fact, they point to its value. Since so many patients once toxic will again have toxemia, prenatal care becomes of paramount importance, for the incidence of severe toxemia can undoubtedly be reduced. Also it should be emphasized that our data concern only the recurrence of toxemia. The data for all cases, including 116 eclamptic patients pregnant again, are set forth in Table XVI.

Fruitfulness of Later Pregnancies.—Among the 466 patients who have been re-examined recently, 200 have had 247 pregnancies since 1935 or 1936. Of these 247 pregnancies, 190 (76.9 per cent) were live births, 44 (17.8 per cent) were abortions, and 13 (5.3 per cent) were stillbirths. Of the 203 pregnancies carrying past the twenty-fourth week, 93 (45.8 per cent) were again toxic, 108 (53.2 per cent) were normal, and 2 were uncertain.

Four mothers (2 per cent) died in the subsequent pregnancy.

GENERAL DISCUSSION

Our analysis demonstrates that about half of all nonconvulsive toxemia patients have hypertension when re-examined three and one-half to five and one-half years after the toxemia, at a time when temporary eleva-

hypertension rises with age in the population as a whole. Whether the *age when toxic* has an effect we can not say, since the follow-up period is nearly the same for all patients. The data for preeclampsies are shown in Table XI.

TABLE X. BLOOD PRESSURE AND PROTEINURIA IN THE PUERPERIUM AS RELATED TO THE REMOTE PROGNOSIS

STATUS IN PUERPERIUM	RECURRENCE OF TOXEMIA		STATUS AT FOLLOW-UP	
	CASES	PER CENT TOXIC	CASES	PER CENT HYPERTENSIVE
Blood pressure normal at 10 days	103	26.22	204	36.77
Blood pressure elevated at 10 days	43	60.50	101	39.60
Proteinuria less than 2 g/L at 10 days	134	34.35	286	38.12
Proteinuria more than 2 g/L at 10 days	8	50.00	22	31.81
Blood pressure normal at 6 weeks	79	26.58	150	27.33
Blood pressure elevated at 6 weeks	15	73.32	43	62.80

TABLE XI. AGE AT FOLLOW-UP IN RELATION TO THE INCIDENCE OF HYPERTENSION AND TO THE RECURRENCE OF TOXEMIA

	AGE AT FOLLOW-UP					
	BELOW 25	26 TO 30	31 TO 35	36 TO 40	41 TO 45	46 PLUS
Incidence of hypertension at follow-up	25.0%	26.7%	38.1%	53.6%	61.3%	77.8%
Recurrence of toxemia	15.7%	51.2%	54.5%	61.1%	71.4%	50.0%

Weight/Height Ratio at Follow-Up.—The greater the body weight relative to the height, the greater the incidence of high blood pressure at follow-up, and the greater the likelihood of toxemia recurrence. The increase is regular in all of the classes of toxemia. The data for pre-eclamptic patients are given in Table XII. Possibly weight control in patients who have had toxemia of pregnancy would reduce the incidence of subsequent hyperpiesia.

TABLE XII. THE EFFECT OF THE WEIGHT/HEIGHT RATIO UPON THE INCIDENCE OF HYPERTENSION AT FOLLOW-UP AND UPON THE RECURRENCE OF TOXEMIA

WEIGHT HEIGHT', LB./INCH	LESS THAN 1.80	1.81 TO 2.00	2.01 TO 2.20	2.21 TO 2.40	2.41 TO 2.60	2.61 TO 2.80	MORE THAN 2.81
Incidence of hypertension at follow-up	15.4%	15.9%	22.4%	40.0%	60.0%	53.9%	62.7%
Recurrence of toxemia	45.5%	30.4%	12.5%	33.3%	50.0%	60.0%	68.2%

Subsequent Pregnancies.—Perhaps one of the most important practical considerations is what advice to give a patient with toxemia, concerning future pregnancies. In our patients, subsequent *normal* pregnancies are associated with a low incidence of hypertension at follow-up. But another toxemia will increase the probability of later high blood pressure. In the pre-eclamptic patients we found the data as shown in Table XIII.

Since many of our pre-eclampsia patients had had pregnancies previous to the toxic gestation of 1935 or 1936, we have made a further analysis of the effect of other pregnancies and toxemias upon the remote prognosis. Here again it is evident that the chances for appearance of future hypertension are augmented by a second toxemia. The data for pre-eclamptic patients are shown in Table XIV.

tions may be expected to have subsided and before advancing age has had a maximum effect.

Many factors are correlated in more or less significant degree with the incidence of hypertension as found at this time. These factors may be considered in three groups, according to our ability to influence them, and thus postpone (or possibly even prevent) later hypertension.

1. Factors beyond our control:
 - a. Family history of cardiovascular renal disease.
 - b. Initial blood pressure level ante partum.
 - c. Age when toxic.
 - d. Age at follow-up.
 - e. Parity at time of toxemic pregnancy.
2. Factors which may possibly be modified:
 - a. The severity of the toxemia, and therefore
 - b. the status at ten days and six weeks post partum.
 - c. The weight-height ratio at follow-up.
3. Factors which can be modified.
 - a. Duration of the toxemia.
 - b. Subsequent toxemia.

Fortunately these latter factors are those with a most profound effect on subsequent hypertension, and give opportunity for reduction of the incidence of high blood pressure in posttoxemic women.

Since the incidence of posttoxemic hypertension increases so markedly with the duration of the toxemia (Fig. 2), it would appear that the prompt delivery of the toxemic patient whose disease appears any time in the last trimester of pregnancy might reduce the incidence of hypertension by two-thirds, to about 13 per cent. Thus of the 121 women now hypertensive after pre-eclampsia, 80 could have been spared. The remote interests of the mothers are best served by interruption of the pregnancy, and the immediate fetal welfare is similarly improved by prompt delivery after thirty-five weeks. This consideration must be balanced against other factors which will vary from case to case. Induction of premature labor is not always easy, especially in the primigravida in whom pre-eclampsia is most common. Operative interference always carries hazards of morbidity and even maternal mortality, as well as of some fetal loss. Since the policy of the Margaret Hague Maternity Hospital has been conservative, interruption of pregnancy has usually been reserved for the more severe cases of toxemia. Our statistics are not, therefore, suitable for analysis as an approach to the problem of balancing the immediate maternal interest against the remote maternal interests and the fetal interest.

The control of subsequent toxemia appears to lie wholly in advising against subsequent pregnancy in those patients with statistically great chance of subsequent toxemia, as present methods may only modify but not prevent toxemia.

FETAL MORTALITY

Since only the patients who were re-examined in 1940 have been included in the analyses, the fetal mortalities recorded here are not exact. Our chief concern is to determine those factors affecting the

5. Longer duration of toxemia.
6. Greater severity of toxemia as judged by blood pressure.
7. Lesser severity of toxemia as judged by proteinuria.
8. Longer persistence of hypertension in days and weeks after delivery.
9. Increased ratio of weight to height, at follow-up.
10. Other toxic pregnancies.

The recurrence rate of toxemia in subsequent pregnancies is about 46 per cent. The factors affecting recurrence are the same as affect the incidence of later hypertension.

Fetal mortality increases with rising blood pressure, increasing proteinuria, and longer duration of maternal toxemia.

We wish to express our gratitude to Drs. S. A. Cosgrove, J. F. Norton, and E. G. Waters for their criticisms of the typescript. We are also indebted to many physicians who have permitted us to re-examine their private patients. Mrs. E. R. Chesley conducted the follow-up clinic. Most of the blood and urine urea determinations were made by Frances Orsato and Peter Marotta.

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As a result of 1,121,707 marriage loans made from August, 1933 to the end of 1938, enforcement of abortion laws, and several other interesting factors, the birth rate in the Reich had increased from 14.7 to 19.7. The effectiveness of control over abortion is shown in the decrease of abortions per 100 normal births from 103.4 in 1929 to 16.2 in 1936 and 18.1 in 1937.

The authors discuss the sociologic implications of marriage loans and similar devices for increasing the national fertility. A new divorce law is mentioned which has resulted in older men divorcing middle-aged wives and remarrying to rear second families. The German technique appears to be statistically more effective than the methods used in France and other European countries to obtain a deliberate increase in the birth rate.

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mortality which also bear upon the incidence of future hypertension in the mother. These factors are severity and duration of the toxemia.

Fetal mortality increases with either the blood pressure or the proteinuria, or both together. Thus in severe pre-eclampsia, the fetal mortality is more than 5 times that in mild pre-eclampsia (Table I). In all groups of toxemia, except the mild pre-eclamptics, the higher blood pressures and proteinurias are associated with increased fetal loss.

The data bearing upon the duration of toxemia in relation to fetal mortality are derived from the pre-eclamptic groups. In these pre-eclamptic patients, fetal deaths mount with continuing toxemia. Often a patient may be carried along with toxemia, supposedly in the fetal interests, only to have the fetus die in utero. Our data may be summarized, combining mild and severe pre-eclamptics, as shown in Table XVII.

TABLE XVII. THE RISE IN FETAL MORTALITY WITH PROLONGATION OF TOXEMIA

DURATION OF TOXEMIA	LESS THAN 1 WEEK	1 TO 2 WEEKS	2 TO 4 WEEKS	MORE THAN 4 WEEKS
Fetal mortality	2.3%	10.6%	13.9%	20.7%

Thus, we see that the fetal interests coincide with the remote maternal interests, in that prolonged toxemia is deleterious to both.

SUMMARY AND CONCLUSIONS

We have re-examined, in 1940, 466, or 72 per cent, of all patients with nonconvulsive toxemias (exclusive of vomiting) who were admitted to the Margaret Hague Maternity Hospital in 1935 and 1936. The patients have been classified according to the new system recommended by the American Committee on Maternal Welfare.

The gross incidence of hypertension, greater than 140/90, at follow-up is 53 per cent. Among the hypertensives, about 45 per cent have eye ground changes and cardiac enlargement.

Proteinuria of possibly significant degree was found in 5.5 per cent of all cases.

Renal function at follow-up, as measured by urinary specific gravity and urea clearance tests, is normal in at least 93 per cent of the patients.

Since the toxic pregnancy of 1935 or 1936, diabetes has appeared in 10 patients; in 2 others diabetes was recognized at the time of the toxemia.

An analysis has been made of some of the factors associated with and possibly contributing to the finding of hypertension at follow-up.

The incidence of hypertension after pre-eclampsia, as found at follow-up, increases with:

1. Family history of cardiovascular disease.
2. Increasing blood pressure, even in the low normal range, as found at the first clinic visit.
3. Increasing age at time of toxemia (or at follow-up).
4. Earlier time in pregnancy of onset of toxemia (however, time of onset, per se, has no effect).

associates¹⁴ found the active principle of vitamin K to be a quinone. Shortly thereafter, four groups of investigators¹⁵⁻¹⁸ announced the successful synthesis of several antihemorrhagic quinone derivatives. It is now generally agreed that 2-methyl-1, 4-naphthoquinone is the most efficacious quinone derivative and that it is the most potent of the substances known to have vitamin K properties. Ansbacher, Fernholz and MacPhillamy¹⁹ also noted that the natural vitamin is less rapidly absorbed by the animal organism than the synthetic compound. Waddell and Guerry²⁰ likewise found this substance to be as efficacious as vitamin K concentrate in the prevention of hemorrhagic disease of the newborn.

PART I

In the first part of this investigation, we determined the clotting activity in 200 newborn infants. The mothers of 100 of these were given 2 mg. of 2-methyl-1, 4-naphthoquinone (Thyloquinone)* by mouth, one-half to forty-four hours before delivery and a concurrent series of 100 cases in which the mother received no vitamin K therapy was used as a control group. Prothrombin activity estimations were made on each child in both series on the first, second, and fourth days of life. A total of 600 individual determinations, accordingly, were made. These observations demonstrate that vitamin K is of definite value in shortening the prothrombin clotting time in the newborn infant.

The "bedside" technique for estimating prothrombin activity as developed by Smith and his co-workers²¹ was used in this part of our investigation. Although it produces consistently higher values than the more complicated two-stage method developed by the same group,²² it was considered to be sufficiently accurate and to be more practical for clinical use in the newborn. The "bedside" test, like Quick's method²³ measures not only the amount of prothrombin present, but also its rate of convertibility to thrombin. Since both factors are important in the coagulation mechanism, this technique was preferred for our investigation.

The method is as follows: 0.1 c.c. of thromboplastin is placed in a 3 c.c. test tube. Blood, freshly drawn from the infant's external jugular vein, is added up to the 1 c.c. mark. The tube is inverted once and then tilted gently until clotting is complete, as evidenced by a failure of the blood to run down the tube in a changed position. The procedure is repeated on a normal adult as a control and the patient's clotting activity is expressed as a percentage of this normal:

$$\text{Clotting activity (in \% of normal)} = \frac{\text{Clotting time of control}}{\text{Clotting time of unknown}} \times 100$$

In our work, the thromboplastin was prepared by grinding 10 Gm. of ox or rabbit brain or lung and infusing it in 10 c.c. of normal saline solution for two hours. This was preserved in a refrigerator. Since the potency of thromboplastin diminishes with age, a control reading was taken every time the test was performed on a group of patients. If difficulty was encountered in withdrawing blood from the vein, the specimen was discarded and a fresh sample was drawn into a clean needle and syringe. Whenever the prothrombin clotting time of the control was appreciably under twenty-five seconds, the thromboplastin was diluted to bring the value up to this figure. In order to maintain a uniform standard, the same adult control (R. C.) was used throughout our study.

*Furnished through the courtesy of E. R. Squibb & Sons.

VITAMIN K ADMINISTERED TO THE MOTHER DURING LABOR AS A PROPHYLAXIS AGAINST HEMORRHAGE IN THE NEWBORN INFANT*

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THIS investigation has been conducted as two separate studies. Part I consisted of the determination of the prothrombin activity in normal newborn infants together with observations on the alterations in this activity which result from the administration of vitamin K to the mother. Part II was concerned with the practical application of the knowledge gained from the first study. It aimed to show the value of intra-partum vitamin K administration in reducing the incidence of hemorrhage in newborn infants.

LITERATURE

Dam,¹ in 1929, noted that chicks on a fat-free diet developed hemorrhagic disease. Later, Almquist² described the same tendency. In 1934, Dam and Schönheyder³ were able to demonstrate that the antihemorrhagic factor necessary for the prevention of this disease was not to be found in any of the then known vitamins. However, they found that the unknown factor could be supplied by adding cereals and seeds common to the ordinary chick diet. Further work by Dam⁴⁻⁶ revealed that green leafy plants, such as kale, alfalfa, and spinach were excellent sources of this antihemorrhagic factor and suggested the term "vitamin K" for this new food element. Subsequently, Schönheyder⁷ proposed that the retardation of coagulation in vitamin K-deficient animals was due to hypoprothrombinemia.

Brinkhous, Smith and Warners⁸ observed that otherwise normal newborn infants sometimes have relatively low prothrombin levels. In the same paper, they reported a case of hemorrhagic disease of the newborn in which the prothrombin value was less than 5 per cent of normal. Subsequent studies by this group⁹ revealed that hypoprothrombinemia is physiologic from the second to the sixth day of life, i.e., during the period in which hemorrhagic disease of the newborn manifests itself. Hellman and Shettles¹⁰ observed even lower levels of prothrombin in premature infants. This may help to account for the frequency with which intracranial hemorrhage complicates prematurity.

Waddell and Guerry,¹¹ in 1939, studied the effect of vitamin K on newborn infants. They administered vitamin K concentrate to alternate children in a series of twenty cases and observed that those who received the concentrate had a more rapid clotting time. They also reported "encouraging results" when this preparation was given in the antenatal period. In a preliminary report consisting of a relatively small number of observations, Hellman and Shettles¹⁰ stated that "extremely low infant prothrombin levels can be raised by feeding vitamin K to the mother prior to delivery or directly to the infant after birth." Later, Shettles, Delfs and Hellman¹² reported that they were able to produce a normal adult prothrombin level in most newborn infants by feeding vitamin K concentrate to the mother during labor.

Although the chemical composition of vitamin K was not then known, Almquist,¹³ in 1936, described a method for its isolation in concentrated form. Doisy and his

*Read at the New York Obstetrical Society, December 10, 1940.

TABLE II. EFFECT OF VITAMIN K ON THE PROTHROMBIN ACTIVITY, FIRST DAY (EXPRESSED AS A PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY). 100 CASES

PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY	FIRST DAY OF LIFE	
	CONTROL CASES	VITAMIN K CASES
10- 20	-	-
20- 30	-	-
30- 40	6	-
40- 50	7	1
50- 60	7	2
60- 70	21	4
70- 80	28	10
80- 90	16	20
90-100	9	27
100-110	4	27
110-120	2	3
120-130	-	4
130-140	-	2
Total	100	100
Mean	73.2% of normal	94.8% of normal

TABLE III. EFFECT OF VITAMIN K ON THE PROTHROMBIN ACTIVITY, SECOND DAY (EXPRESSED AS A PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY). 100 CASES

PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY	SECOND DAY OF LIFE	
	CONTROL CASES	VITAMIN K CASES
10- 20	1	-
20- 30	6	-
30- 40	8	-
40- 50	14	3
50- 60	19	5
60- 70	18	3
70- 80	17	4
80- 90	8	33
90-100	6	25
100-110	3	20
110-120	-	5
120-130	-	1
130-140	-	1
Total	100	100
Mean	61.1% of normal	90.8% of normal

K to the mother accordingly causes the newborn infant's blood to clot as readily as that of a normal adult.

Table IV shows the values for the vitamin K cases and the controls on the fourth day of life. Here again there is a great reduction in the number of infants with low values after the use of vitamin K during labor. The lowest value obtained in any of the 100 cases was 38 per cent of normal, and all but 5 of the remaining 99 infants showed clotting activity equal to 50 per cent of normal or over during the first four days of life. None of the 100 vitamin K cases showed any evidence of hemorrhage. It would seem, therefore, that vitamin K eliminates the physiologic bleeding tendency at birth, by preventing the customary fall in prothrombin values on the second day, and by maintaining values which approach those of the normal adult during the early days of life when little or no vitamin K is available to the infant.

Comparison of the prothrombin values on the first, second, and fourth days with the results which followed the prophylactic administration of vitamin K to the moth-

TABLE I. PROTHROMBIN ACTIVITY ON FIRST, SECOND, AND FOURTH DAYS OF LIFE (EXPRESSED AS A PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY). 100 CASES

PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY	A FIRST DAY NUMBER OF CASES	B SECOND DAY NUMBER OF CASES	C FOURTH DAY NUMBER OF CASES
10-20	-	1	1
20-30	-	6	4
30-40	6	8	6
40-50	7	14	7
50-60	7	19	8
60-70	21	18	17
70-80	28	17	29
80-90	16	8	15
90-100	9	6	8
100-110	4	3	4
110-120	2	-	1
Total	100	100	100
Mean	73.2% of normal	61.1% of normal	72.4% of normal

Variations in clotting activity (expressed as a percentage of adult normal clotting activity) observed on the first, second, and fourth days of life are shown in Table I. The values for the first day in 100 cases are given in the second column (A) and those for the second and fourth days are similarly tabulated in the third (B) and fourth (C) columns. On the second day, the clotting activity was less than 20 per cent of normal in one infant and from 20 to 30 per cent of normal in 6 other cases. Extremely low values persisted beyond the fourth day in 5 of these 7 infants. Of the 8 patients who had values of 35 per cent of normal or under, 4, or 50 per cent, showed evidence of hemorrhage; on the other hand, no bleeding occurred in any of the infants whose clotting activity was above this value. Although marked variations in prothrombin activity are shown by the values for each day, comparison of the figures in the three columns indicates, first, that normally the prothrombin activity diminishes rapidly on the second day and that this loss is, to some extent, regained by the fourth day. In other words, the number of infants showing clotting activity below 60 per cent of normal increased from 20 on the first day to 48 on the second and returned to 26 by the fourth day. Similar conclusions may be drawn from the mean values for each day. The mean clotting activity for the first day was 73.2 per cent of normal in the 100 cases. This fell to 61.1 per cent on the second day and returned to 72.4 per cent on the fourth day.

Table II illustrates the effect of vitamin K administered to the mother during parturition. The second column of this table represents the normal clotting activity values on the first day of life while the third column represents the values obtained in 100 infants whose mothers received vitamin K during labor. After the administration of vitamin K, only 3 infants showed clotting activity below 60 per cent of normal in contrast with 20 who did not have this prophylaxis.

The value of vitamin K as a means of increasing prothrombin activity in the newborn infant is still better shown in Table III. The figures in Column 2 show the control cases and those in Column 3 represent the infants of the mothers who received vitamin K during labor. In spite of the normal fall in prothrombin activity which occurs on the second day of life, only 8 infants who had received vitamin K had values for clotting activity below 60 per cent of normal while the control cases in this low field numbered 48. Since hemorrhage is most likely to occur in these infants with low prothrombin values, vitamin K used prophylactically reduced this risk in infants especially predisposed to bleeding to almost one-sixth of what it would have been without this prophylactic measure. The values in Column 3 so closely approach the normal adult values that we are justified in stating that vitamin K administered to the mother during labor prevents the customary drop in prothrombin activity which is seen soon after birth. The administration of vitamin

TABLE IV. EFFECT OF VITAMIN K ON THE PROTHROMBIN ACTIVITY, FOURTH DAY (EXPRESSED AS A PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY). 100 CASES

PERCENTAGE OF NORMAL ADULT PROTHROMBIN ACTIVITY	FOURTH DAY OF LIFE	
	CONTROL CASES	VITAMIN K CASES
10- 20	1	-
20- 30	4	-
30- 40	6	1
40- 50	7	-
50- 60	8	5
60- 70	17	6
70- 80	29	13
80- 90	15	18
90-100	8	21
100-110	4	26
110-120	1	7
120-130	-	3
Total	100	100
Mean	72.4% of normal	93.3 per cent of normal

28, and 35 per cent, respectively, of normal on the fourth day had bloody stools or vomited small amounts of bloody mucus on the same or on the following day. Hemorrhage did not occur in any infant whose prothrombin was normal on the fourth day. Four infants whose mothers received the drug less than an hour before delivery had clotting activity values similar to those of the control group. It, therefore, seems reasonable to conclude that the drug should be administered at least one hour before delivery if any beneficial effect is to be obtained.

The results in this part of our investigation seem to indicate that vitamin K prevents the hypoprothrombinemia which normally occurs from the second to the fourth or fifth day of life. They also indicate, as has been suggested by Quick,²⁴ that hemorrhagic disease of the newborn may be due to a failure of the plasma prothrombin levels to return to normal.

PART II

The second part of our investigation was undertaken to show the truth or falsity of the foregoing conclusions by observing the change in the incidence of hemorrhagic conditions which might follow the administration of vitamin K to a fairly large number of parturient women.

Two milligrams of 2-methyl-1, 4-naphthoquinone (Thyloquinone) were given to alternate mothers in a series of 2,059 cases. Of these, 1,037 were used as controls and 1,022 received vitamin K. Because some of the patients were too far advanced in labor at the time of admission to be of value in the vitamin K study, the control group contained 15 more cases than the vitamin K series.

Table V shows the site of hemorrhage and also gives the type of delivery and weight of the control infants. The same data are recorded for the vitamin K cases in Table VI. A summary showing the incidence of hemorrhage in the full-term and premature infants of both series is furnished in Table VII. In the control group of 1,037 cases, 21, or 2 per cent, revealed some evidence of hemorrhage, while only 5, or 0.5 per cent, of the 1,022 vitamin K cases had any signs of bleeding. From our clinical observations in this large series of cases, therefore, it would seem that the use of vitamin K during labor reduced the incidence of hemorrhage in the newborn infant approximately 75 per cent.

ers, is facilitated by the graphs shown in Fig. 1. The three above the midline (A, B, C) represent the scatter of the control groups and those inverted below this line (D, E, F) show the distribution of the vitamin K cases. As might be expected in a series of this size, there is a wider scatter in all the graphs. However, a definite shift toward higher values in the vitamin K cases, as compared with the controls,

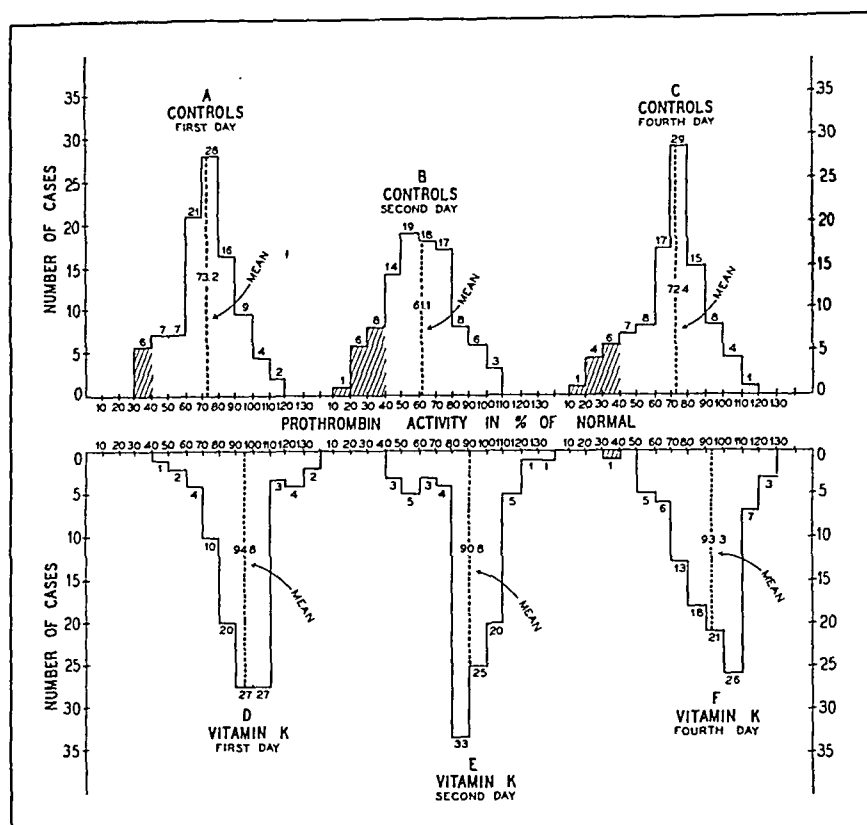


Fig. 1.—The upper three graphs represent clotting activity in 100 control cases on the first (A), second (B) and fourth (C) days. The number of cases are plotted perpendicularly while the horizontal figures show the percentage of normal clotting activity. The number of cases for each 10 per cent variation accordingly are blocked out in each of the three polygons. The mean percentage of normal clotting activity for each group is represented by the dotted line. The shaded areas indicate the clotting activities which fell below 40 per cent of the normal and were thus in the potential hemorrhage field. These three upper figures graphically show that the clotting activity is considerably diminished on the second day and tends to return toward normal by the fourth day of life.

The three inverted graphs represent the vitamin K cases on the first (D), second (E), and fourth (F) days. Aside from the fact that they are inverted, they are plotted in a manner similar to the upper graphs. They, therefore, show a definite shift to the right which illustrates the rather marked increase in prothrombin activity that results from the prophylactic use of vitamin K. In only one of the 300 observations (Graph F), did the clotting activity fall within the potential hemorrhage range, i.e., below 40 per cent of normal.

Comparison of the three inverted graphs also shows that the use of vitamin K tends to prevent the rather marked fall in prothrombin which normally occurs on the second day of life.

is evident. Not only do these higher values prevail but also the means of the 3 vitamin K graphs are nearly constant in contrast with the second day drop in the control group.

We have found no correlation between the prothrombin activity and sex, race, presence and degree of jaundice. One of our control cases developed erythroblastosis fetalis with icterus gravis. This infant's prothrombin activity was normal in each of the three observations. Four other controls who had prothrombin values of 17, 21,

incidence of hemorrhage in infants born before term, and we anticipate as a result a considerable reduction in the death rate of our prematurely born infants.

SUMMARY AND CONCLUSIONS

1. Clotting activity was studied on the first, second, and fourth days of life in a series of 200 infants. Vitamin K was given during labor to the mothers in alternate cases. We were able, therefore, to compare the effects of its administration in 100 cases with a similar number of controls.

2. A study of the control infants shows that, on the first day of life, clotting activity is approximately 70 per cent of that which is observed in normal adults.

3. A physiologic fall in prothrombin usually occurs on the second day. This fall at times may reach dangerously low levels.

4. Fifty per cent of the infants whose clotting activity fell below 35 per cent of normal values showed evidence of hemorrhage.

5. By the fourth day, clotting activity values tend to approach the level of those observed on the first day of life and are said to reach this level by the sixth day.

6. Clotting activity approaching that observed in the normal adult may be obtained on the first day by the prophylactic administration of vitamin K to the mother during labor.

7. Vitamin K, administered to the mother during labor, also prevents the physiologic fall in prothrombin values which is commonly observed on the second day of life.

8. Only one infant in a series of 100 whose mothers received vitamin K during labor, had a low value for clotting activity and, in this instance, it was 38 per cent of the normal adult value on the fourth day only.

9. The use of vitamin K during labor and antenatally should prevent some of the hemorrhages which occur in the newborn infant.

10. Only 5, or 0.5 per cent, of 1,022 infants whose mothers received vitamin K showed any evidence of hemorrhage in contrast with 21, or 2 per cent, of 1,037 control cases.

11. In this series of 2,059 cases, the alternate mothers of which received vitamin K, it appears that this drug reduced the incidence of hemorrhage approximately 75 per cent in the newborn infant.

12. Vitamin K, accordingly, should be very valuable in reducing the incidence of hemorrhage in all newborn infants. This should be especially true when they are born prematurely or after long labors and difficult operative procedures.

We wish to express our thanks to Drs. W. B. Henderson, D. A. Connors, and L. E. Mendonsa, residents on the College divisions at Kings County and Greenpoint Hospitals, for their assistance in the conduct of these investigations.

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TABLE V. HEMORRHAGIC CONDITIONS OBSERVED IN 1,037 CONTROL INFANTS

NO.	TYPE OF DELIVERY	WEIGHT (GRAMS)	SITE OF HEMORRHAGE
1	Spontaneous	1680	Intracranial hemorrhage
2	Spontaneous	3140	Bloody stools two days
3	Spontaneous	2560	Intracranial hemorrhage
4	Spontaneous	3640	Bloody stools fourth day
5	Low forceps	3000	Intracranial hemorrhage
6	Spontaneous	2940	Intracranial hemorrhage
7	Spontaneous	1620	Intracranial hemorrhage
8	Spontaneous	2620	Bloody stools sixth day
9	Spontaneous	2960	Intracranial hemorrhage
10	Spontaneous	1780	Intracranial hemorrhage
11	Spontaneous	3580	Bloody stools third and fourth days
12	Spontaneous	2500	Intracranial hemorrhage
13	Breech	1160	Intracranial hemorrhage
14	Spontaneous	3100	Bloody stools third to fourteenth day
15	Spontaneous	3160	Intracranial hemorrhage
16	Breech	3560	Intracranial hemorrhage
17	Spontaneous	3180	Bloody stools fourth day
18	Breech	1590	Intracranial and adrenal hemorrhage
19	Spontaneous	2900	Intracranial hemorrhage
20	Spontaneous	2560	Intracranial hemorrhage
21	Spontaneous	4200	Bloody stools second, third, fourth, and fifth days

TABLE VI. HEMORRHAGIC CONDITIONS OBSERVED IN 1022 VITAMIN K INFANTS

NO.	TYPE OF DELIVERY	WEIGHT (GRAMS)	SITE OF HEMORRHAGE
1	Low forceps	3500	Intracranial hemorrhage
2	Spontaneous	2920	Intracranial hemorrhage
3	Spontaneous	3200	Bloody stools third day
4	Cesarean section Placenta previa	1880	Intracranial hemorrhage
5	Spontaneous	1840	Intracranial hemorrhage

TABLE VII. SUMMARY OF END-RESULTS FOLLOWING THE USE OF VITAMIN K DURING LABOR

	CONTROL CASES		VITAMIN K CASES	
	NO. OF INFANTS	HEMORRHAGE CASES	NO. OF INFANTS	HEMORRHAGE CASES
Full term infants	981	16 or 1.6%	985	3 or 0.3%
Premature infants	56	5 or 9.0%	37	2 or 5.4%
	1037	21 or 2.0%	1022	5 or 0.5%

Since no ill-effects were observed from the administration of this preparation to any of our patients, we are now giving 2 mg. of vitamin K at the time of admission and are repeating the dose at six-hour intervals throughout the labor. In this way, we hope to facilitate the transmission of the drug in amounts sufficient to assure the presence of adequate prothrombin activity in all newborn infants. Because the tendency to diminished clotting activity is greater in prematurely born children, it is our custom to repeat the drug every four hours in all premature labors. We hope by this means to reduce the all too frequent

be difficult to prove. Prolonged labor is of great significance. We found in a study of at least 700 infants delivered by cesarean section that there were no cases of hemorrhagic disease in the infants delivered without labor. The mother of one infant had sixty hours of labor before delivery, and this infant developed hemorrhagic disease. That creates the interesting hypothesis that even if all infants have a low prothrombin level at birth, there is still necessary a second factor, namely the trauma of labor. All infants then, of mothers with a prolonged labor, will probably be benefited by the antenatal administration of vitamin K to the mother.

DR. ONSLOW A. GORDON.—I would like to ask Dr. Beck how much vitamin K was given and when it was given during the course of labor.

DR. SAMUEL A. WOLFE.—I would like to ask if vitamin K is of any value in cerebral hemorrhage of the newborn infant if the prothrombin level is above 40 per cent of the average value.

DR. I. C. RUBIN.—I would like to ask Dr. Beck if he has found a single case of erythroblastosis in his series, and if not, would he venture any expression of opinion with regard to the administration of vitamin K in such cases if met with?

DR. ARCHIE BLACK.—The possibility of hyperprothrombinemia from excessive amounts of vitamin K has been raised. As far as I know, no evidence has been reported of the existence of such a condition. Some of the European workers have administered very large doses of this naphthoquinone to human beings, in some instances one hundred times as much as Dr. Beck has used, and they have not observed any such condition.

DR. BECK (closing).—You may recall that in my paper I stated that different results are obtained when the various tests are used. This, however, has no bearing as far as our observations are concerned, since we used the same test throughout all of our work. We did have a relatively high incidence of hemorrhage cases. These were not typical cases of melena neonatorum but in all of them a diagnosis of bleeding of some character was made. In our Clinic, we observed a rather high incidence of these bleeding cases long before we knew anything about vitamin K. Because a very large proportion of our service patients were in the low economic group, we thought that this bleeding tendency might be due to some dietary deficiency. Since we have been using vitamin K, on the other hand, there has been a great diminution in the same types of hemorrhage. As both vitamin K cases and the control series were analogous in other respects, we believe that our results show the beneficial effects of vitamin K; in spite of the fact that our control series had more hemorrhages than is usually observed in those clinics whose patients belong to the higher economic groups. I think this question of diet also accounts for the great difference between the incidence of bleeding in our private and ward patients. The private patients, as in Dr. Holladay's practice, no doubt received a balanced diet throughout their pregnancy and, as a result, were less liable to have this deficiency.

We gave 2 mg. of thyloquinone in the course of the labor. Its cost, I think, is about two cents per dose. As it can do no harm and may do considerable good, we think that it should be used routinely in private as well as ward cases. In most instances, it was given at least one hour before delivery. We recommend, however, that it might be better to administer the drug every six hours throughout the labor.

In answer to Dr. Bunzel's query concerning the criteria for hemorrhage, I would like to say that any type of bleeding was regarded as hemorrhage in the newborn infant. As our tabulations show, most of the hemorrhages were either intracranial or from the intestinal tract. In the majority of instances of intracranial hemorrhage, the diagnosis was made at autopsy. All diagnoses were made by the pediatricians and they did not know which mothers had received vitamin K. The same criteria and the same physicians therefore were used in both the control and the vitamin K cases. Our deductions, as a result, should be correct.

This preparation has been recommended for use during the ante-partum period by some men. We have been reluctant to use it at this time because of the increased coagulability of the blood which is noticed in cases of eclampsia. After the

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DISCUSSION

DR. E. STEWART TAYLOR (by invitation).—The important thing that should be emphasized is that 50 per cent of the control infants, who had a clotting activity below 35 per cent of normal, had hemorrhage of some variety. On the other hand, in the 100 vitamin K cases, there was only one which had a low prothrombin clotting value and no case showed evidence of hemorrhage.

DR. ARCHIE BLACK (by invitation).—There seem to be two important sources of vitamin K in Nature, one from foods, particularly the green vegetables, such as spinach and alfalfa, and the other from bacteria. Apparently, the bacteria in the intestinal tract contribute considerably. It has been suggested by Quick and several others that the prothrombin content of the blood of the newborn infant begins to rise from the third to the fifth day, because it requires that long for the bacterial flora to be established in the intestinal tract and to produce sufficient vitamin K.

The known vitamin K's that exist in Nature are all chemical derivatives of 2-methyl-1, 4-naphthoquinone. It was a very interesting discovery that this simple compound is more active than either of the two vitamins found in Nature, the one from alfalfa and spinach and the other which is produced by bacteria.

DR. CARL T. JAVERT (by invitation).—The evaluation of the prothrombin concentration in the blood, from the standpoint of various tests, including the older one of Howell, gives values with great apparent variance. If you use the Smith or the Quick test, you find relatively normal or slightly subnormal values in the prothrombin level in the blood of the infant. On the other hand, if you use the Warner, Brinkhouse, and Smith test, the two-stage test which was referred to, you find that the prothrombin level in the cord blood of newborn infants is decidedly low. In relation to an adult with 100 per cent of normal, the newborn infant may have as little as 20 per cent.

It is surprising that many infants with a low prothrombin do not develop hemorrhagic disease. We have seen levels as low as 5 per cent of normal and less, in terms of the Warner, Brinkhouse, and Smith test, without hemorrhagic disease.

It was interesting to me to see in the control cases of this series that there was an incidence of hemorrhagic disease as high as 2 per cent. In our own clinic the average incidence of hemorrhagic disease is about the same as in Dr. Beck's vitamin K treated patients, namely, 0.7 per cent. This incidence is borne out by observations of Townsend as far back as 1894, and more recently by Salmonson in Norway, as well as by reports from other parts of the world. With an incidence of hemorrhagic disease of 1 per cent or less, the effectiveness of vitamin K or any other preparation for the further reduction of the incidence of hemorrhagic disease may

Although a great deal of work has been done with amplification of heart sounds (adult, child, and fetus), very few studies have been reported of the actual recording of these sounds by the stethograph or a similar instrument.

Recently, McKee^{10, 11} reported interesting studies of heart sounds in normal children, and heart sounds and murmurs in children with rheumatic heart disease by means of the stethograph. Smith¹² studied fetal heart sounds in 52 cases by the use of a recording instrument, and was able to reproduce the amplified sounds by means of phonograph discs.

Originally it was shown that the electric energy of the fetal heart was too weak, in relation to that of the maternal heart, to be demonstrated on an electrocardiogram when usual methods were used. Therefore work was done on animals whose fetus was larger than the human fetus.

Nörr,¹³ and Steffan and Strassman,¹⁴ studied domestic animals especially the horse, and the latter developed a satisfactory technique which they used on pregnant women. There are a few scattered studies on the human fetal electrocardiogram by Sachs,¹⁵ Maekawa and Toyoshima,¹⁶ and Strassman.¹⁷ In 1938, Strassman¹⁸ and Mussey¹⁹ were able to report on the improved technique and results of routine fetal electrocardiography during pregnancy. They studied 52 gravidas on whom 70 fetal electrocardiograms were taken, and found 87 per cent positive fetal electrocardiograms and 13 per cent negative tracings.

At about the same time (1938), Bell¹ studied a series of 33 cases of fetal electrocardiograms by using a fundus-symphysis pubis lead with the thermionic valve technique, a valve electrocardiograph to which a balanced input amplifier was introduced. This instrument gave as much amplification as could be obtained without oscillation. Of the 33 cases that he examined in the last two months of pregnancy, about one-third showed positive results. He suggests that the failure to secure positive results in all cases is due partly to the differences in the electric properties of the abdominal wall, and partly to the electrical disturbances produced by the abdominal muscles, and not to insufficient sensitivity of the apparatus or to differences between the fetus.

Occasional cases²⁰ have been reported of the accidental detection of fetal electrocardiograms while doing a routine maternal electrocardiogram.

PURPOSE

The purpose of this study is to develop a positive method by the use of a simple technique for determining during pregnancy and labor whether or not the fetus is alive. It occurred to us that if information concerning the status of the fetal heart could be gained by the recording of fetal heart sounds and fetal electrocardiograms individually, much more could be learned by a combined study, both for practical teaching and research purposes. Records obtained by any method should be accurate as well as easy to interpret.

With this in mind, the principles promulgated by Strassman^{18, 19} for the study of the fetal electrocardiogram were adhered to in this combined study. These principles are: (1) To avoid modification of the electrocardiographic apparatus which was generally in use; (2) not to employ unusual leads, such as placing electrodes in the rectum or vagina, or fundus-symphysis pubis leads as used by Bell; (3) to increase the amplitude of the waves and decrease shakiness and fuzziness of the tracings as far as possible.

pregnancy has reached term and the patient has gone into labor, we do not think that the administration of vitamin K should have any deleterious effect in this regard.

Vitamin K, I believe, was first used in infants after birth. Its hypodermic administration is very valuable in those cases in which the prothrombin values are low. It certainly should be used whenever hemorrhage occurs or whenever the type of delivery leads us to anticipate hemorrhage. In other words, after prolonged labors and operative deliveries, this prophylactic use of vitamin K should be of value. Because of the increased tendency toward hemorrhage in prematurely born infants, the prophylactic administration of vitamin K also is recommended whenever a child is born before term, even though it be delivered by cesarean section.

In reply to Dr. Wolfe, I would say that I doubt very much whether vitamin K would be of any use in the patient who has a high prothrombin value.

We have noted an increase in the incidence of erythroblastosis in our clinic. This may, of course, be due to the fact that we are on the lookout for this condition and, as a result, make better diagnoses than in former times. Because our patients belong in the low economic group, however, we have thought the increase in this condition also might be due to some deficiency. Replying to Dr. Rubin, I might say that one of the control cases had erythroblastosis. In this instance, however, there was no reduction in the prothrombin values.

FETAL ELECTROCARDIOGRAPHY AND STETHOGRAPHY

A COMBINED STUDY

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INTRODUCTION

AS FAR as we know, no attempt has been made to study the human fetal electrocardiogram and stethogram simultaneously. Bell,¹ in his discussion of the only twin pregnancy recorded by the fetal electrocardiogram, presents arguments to prove that the waves produced are fetal waves; and concludes his discussion with the statement that completely satisfying proof could be given only by simultaneous records of fetal heart sounds and fetal electrocardiograms.

Many contributions have been made and various methods used in the study of fetal heart sounds.²⁻⁹ Originally, amplification of heart sounds was done on adults and its practicability was demonstrated. Pommerenke and Bishop⁴ used an instrument for the amplification of fetal heart sounds with good room volume, clarity, and freedom from distortions. They were able to obtain sufficient output from the amplifier to cut satisfactory phonograph discs. DeCosta⁵ was able to reproduce the rate and regularity of fetal heart sounds by means of the photostethoscope, an instrument consisting of a small neon lamp which translates sounds into flickers of light.

Electric stethoscopes, various microphones, thermionic valves, and amplifying and reproducing apparatus⁶⁻⁹ have been used by many workers to demonstrate fetal heart sounds.

detect fetal heart tones with the ordinary stethoscope, apply the microphone to all four quadrants of the abdomen, listening at each quadrant by means of the stethophone for fetal heart sounds. By this method we were able to detect sounds in almost all cases; (5) if no sounds are detected, record a tracing from each quadrant; and (6) if sounds are detected, record a tracing from that particular area.

Having completed all connections, the fetal electrocardiogram and stethogram are recorded separately and simultaneously. In routine electrocardiography, the speed of the film is 25 mm. per second. This speed is used for the simultaneous recording. Ordinarily, a speed of 50 to 75 mm. per second is used in stethography. We used this speed in studying the heart sounds separately.

Electrocardiographic tracings are first taken with the usual leads (I, II, and III). The electrode is then changed from the left thigh to the right thigh, and the tracings are repeated with Leads II and III (right arm-right thigh, left arm-right thigh, respectively). These five leads (right arm-left arm, right arm-left thigh, left arm-left thigh, right arm-right thigh, left arm-right thigh) cover the main directions the axis of the fetal heart might take in the body of the mother, projected on a two dimensional field. The usual electrocardiographic standardization is used; 1 millivolt deflects the string 1 cm. Two feet of film are used for each lead in order to facilitate study of the tracings.

It is a general physiologic fact,²³ that the first sound in adults is heard very shortly after the beginning of systole and the second sound immediately after the end of systole. The first sound is therefore systolic, and the second sound diastolic. In the stethograms studied, the systolic phase is measured from the beginning of the first sound to the end of systole, and the diastolic phase, from the beginning of the second sound to the end of diastole.

MATERIAL

This paper is a preliminary report of the study of the fetal electrocardiogram and stethogram during pregnancy. In a subsequent paper we will report on the results during labor, and add more cases during pregnancy.

Forty gravidas were drawn at random from the outpatient obstetric clinic. We had no previous knowledge of the location of the fetal heart, the presentation of the fetus, or the presence or absence of a viable fetus. None of the patients were organic cardiacs, although no attempt was made to discriminate. All patients were in the last two months of pregnancy because of previous knowledge^{18, 19} that better results are obtained with the fetal electrocardiogram, although fetal heart sounds can be recorded as early as the sixteenth week of pregnancy. The patients were studied the day following their last visit to the obstetric clinic in order to correlate the findings of the obstetrician with our own.

After delivery, all necessary data relative to the baby were collected and recorded, as well as the final diagnosis at delivery.

Table I shows the age distribution and parity of the gravidas studied. It is noted that most of the patients are primiparas and in the younger age group.

TABLE I. DISTRIBUTION OF PATIENTS ACCORDING TO AGE AND PARITY

AGE	PARA I	PARA II	PARA III	PARA V	TOTAL
19-23	17	3	1	0	21
24-28	6	4	4	0	14
Over 28	0	4	0	1	5
Total	23	11	5	1	40

RESULTS

All 40 women gave birth to live babies. The stethogram was positive in all, or 100 per cent. In 4 cases the fetal heart tones could not be detected by the ordinary stethoscope. In these there was a loud uterine souffle which interfered with

The physician not infrequently encounters conditions which make it difficult for him to hear the fetal heart sounds by ordinary methods. These conditions are: (1) An obese abdominal wall, (2) an excessive amount of amniotic fluid (hydramnios), (3) an abnormal position of the fetus in relation to the mother's abdominal wall, and (4) the presence of adventitious sounds (uterine souffle).

At other times, operative procedures (craniotomy and cesarean section) may be necessary, and determination of the viability of the fetus is most important. This determination may also be of importance from a medicolegal aspect where the availability of permanent graphic records is necessary.

Many other problems are encountered which may be answered by our combined study. These may include: (1) The presence of twins or multiple pregnancies, (2) the presence of congenital defects of the fetal heart, (3) the effect of pregnancy and labor on the fetal heart under normal and abnormal conditions, and (4) the effect of drugs on the fetal heart.

METHOD

The instrument used in this study is called the electrocardiograph-stethograph.* Tracings of the fetal electrocardiogram and stethogram can be made separately or simultaneously. In the technique for the study of the fetal electrocardiogram, we follow Strassman's method very closely with few exceptions.

The patient is placed flat on her back on a bed, thereby avoiding any muscular contractions that may occur in the sitting position. She is allowed to rest about fifteen minutes before any recordings are done, to permit her to become acclimated. She is assured that there is nothing wrong with her pregnancy in order to allay any anxiety. The room used for this study was carefully selected to avoid extraneous noises and other electrical apparatus which might interfere with the recording of fetal heart sounds and the fetal electrocardiogram. The skin and the electrodes are moistened with saturated saline solution. The electrodes used are the same as those used for routine electrocardiography, and measure $2\frac{1}{2}$ by $1\frac{1}{2}$ inches. The electrodes are placed on the upper arms and the left thigh, and are fastened with bandages 3 inches wide which have been previously soaked in saturated saline solution. The purpose of the position of the electrodes and the use of saline solution is to lessen the skin resistance and to improve the detection of the fetal cardiac impulses.

The stethograph of our instrument was designed by Lockhart and for a detailed review of methods, reference should be made to his papers.^{21, 22} It is an instrument that records sound vibrations as they actually occur, rather than as they are heard. It consists mainly of a microphone, a stethophone, an amplifier, and a recorder. The microphone is equipped with three bells in order to secure various degrees of filtering. The No. 1 bell has a large open face measuring 2 inches in diameter, the No. 2 bell is similar in size but covered with a diaphragm, the No. 3 bell is approximately of the same size as that used on stethoscopes. After trying all three bells, we found that the fetal heart tones can be recorded with the greatest amplitude by the No. 1 bell.

The following is the routine used in the stethographic recording: (1) Listen to the abdomen with the ordinary stethoscope in order to localize the fetal heart sounds; (2) if detected, apply the microphone to that particular area, and hold it in place by means of a rubber belt. The rubber belt must be tight enough to insure a good seal between the bell and skin; (3) listen with the stethophone, clarify the fetal heart sounds by means of the volume control, avoid picking up room noises, and prevent blurring of the light beam shadow; (4) if unable to

*Manufactured by the General Electric Company as the Hindle "All Electric" Model.

was fetal systole greater than diastole. Fetal heart rates above 160 are considered abnormal.³¹

Of the 40 recorded stethograms, the second sound was loudest in 21 (55 per cent), the first sound in 7 (17½ per cent); they were equal in 9 (22½ per cent), and they were variable in 2 (5 per cent), the intensity of sounds varying in different cycles.

In 2 cases, the fetal heart sounds were hardly detectable by the stethogram. In one of these, the fetal electrocardiogram was hardly detectable, and the weight at birth was 5 pounds. The other was an infant delivered by breech which weighed 6 pounds 14 ounces. The size of the fetus may be a factor in the intensity of fetal heart tones.

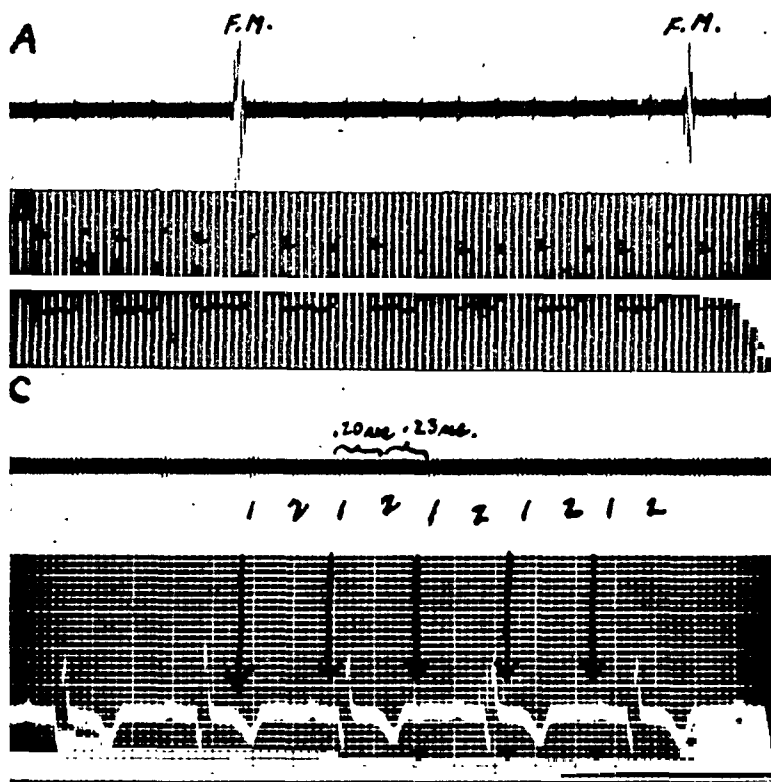


Fig. 2.—Normal fetal heart sounds with film speed of 25 mm. per second. *A*, active fetal movements (*F.M.*). Intensity of sounds appears equal. *B*, sinus arrhythmia. Note differences in the length of the various diastolic phases (compare diastolic phase of cycle 3 with that of cycle 6). Intensity of sounds varies; second is louder but toward end of tracing they appear equal. *C*, simultaneous recording of fetal heart sounds and fetal electrocardiogram. Note fuzzy electrocardiogram tracing but negative fetal waves (vertex presentation), detected with the aid of first sound. First sound louder than second.

There is a definite relationship between maternal and fetal heart rates. The fetal rate is in direct proportion to the maternal rate. The faster the maternal rate, the faster the fetal rate; the slower the maternal rate, the slower the fetal rate. The usual proportion of maternal to fetal pulse in our series is 3:5 or 5:8.

Of the 40 gravidas studied, 34 (85 per cent) were vertex presentations, and 6 (15 per cent) were breech presentations. Fetal electrocardiograms were positive in 32 cases (80 per cent), and were negative in 8 cases (20 per cent). In 27 (79 per cent) of the vertex cases, the fetal electrocardiograms were positive, and in 7 (21 per cent) they were negative. Five of the breech cases were positive

detection by the ear. In one of the above cases, the patient was very obese. The uterine souffle was recorded together with the fetal stethogram in 13 cases, the souffle overlapping fetal systole and diastole. In one case the fetal heart sounds could neither be detected by the ordinary stethoscope nor by the stethophone (microphone), due to a very loud uterine souffle. The sounds were recorded by the stethogram (Fig. 5, *A*). Fetal sinus arrhythmia was present in 4 cases, and fetal movements were well recorded in two (Figs. 1 and 2).

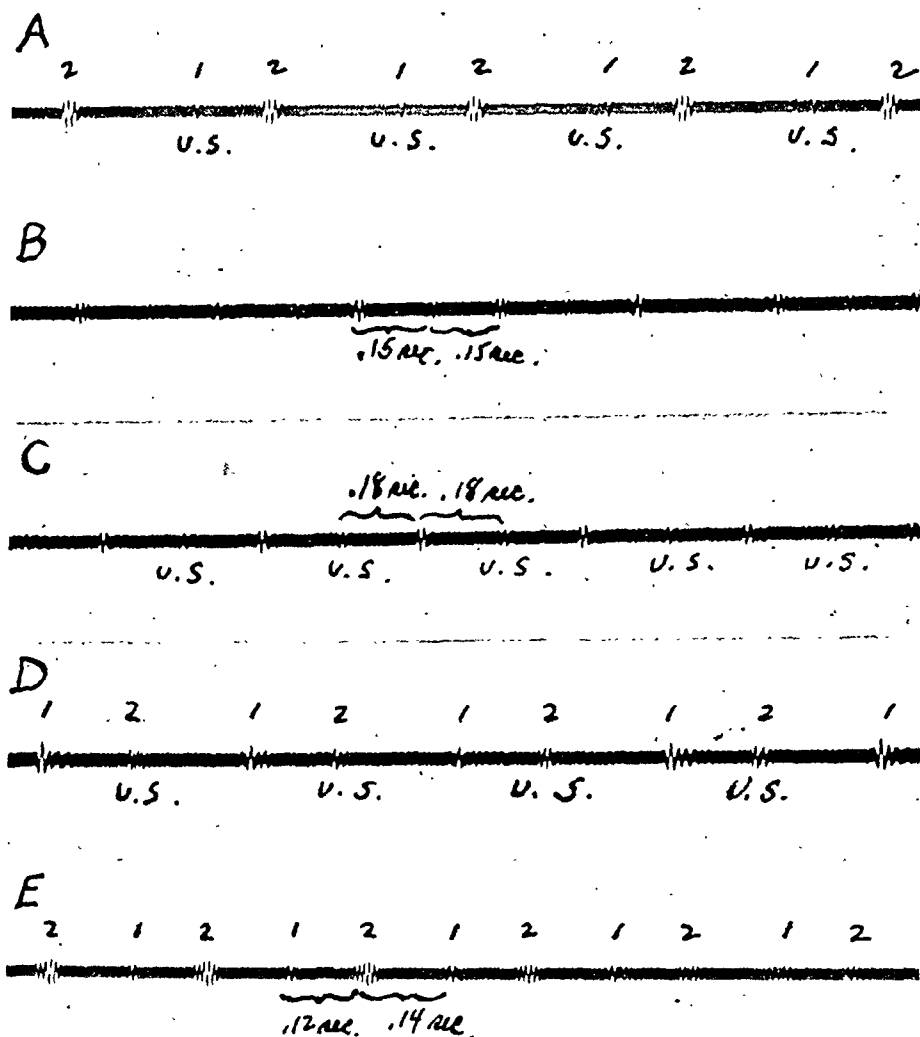


Fig. 1.—Normal fetal heart sounds with film speed of 50 mm. per second. *A*, second sound louder than first. Uterine souffle (U.S.) covers systole and diastole. Systole, 0.16 sec.; diastole, 0.27 sec. Fetal rate, 136. *B*, systolic and diastolic phases of equal length, 0.15 sec. Fetal rate, 200. *C*, systolic and diastolic phases of equal length, 0.18 sec. Fetal rate, 166. Uterine souffle covers both phases. See Fig. 3 for differentiating first from second sound. *D*, first sound louder than second. Note variations in intensity and length of sounds. In third cycle, intensity of first and second sounds appears equal. Systole, 0.20 sec.; diastole, 0.26 sec. Fetal rate, 130. Uterine souffle present. *E*, at the beginning of tracing, second sound louder than first. Near the end, intensities of both appear equal.

The length of fetal systole varied between 0.12 and 0.22 second and fetal diastole between 0.14 and 0.38 second. In 4 cases, the length of systole was equal to that of diastole. In these, the fetal heart rates were 200, 166, 166, and 150 beats per minute, indicating that the more rapid the fetal rate, the shorter the diastole, until systole and diastole may become equal (Fig. 1). This well conforms with the shortening of diastole in tachycardias of adults. In no event

(83 per cent), and one was negative (17 per cent). These figures are slightly less than those of Strassman's series with the exception that our breech cases showed more positive electrocardiograms. We encountered no difficulty in studying breech electrocardiograms (Table II).

There is no difference in the percentage of positive fetal electrocardiograms, whether taken three weeks before delivery or later, provided they are recorded within the last two months of pregnancy. However, there is a definite relationship between the size of the fetus (as evidenced by birth weight) and the number of positive fetal electrocardiograms. The smaller the fetus, the less positive and more negative electrocardiograms are recorded. The larger the fetus, the more positive and less negative electrocardiograms are recorded. The sex of the fetus has no influence on the number of positive electrocardiograms (Table III).

TABLE III. RELATIONSHIP BETWEEN SEX, WEIGHT OF BABY AT BIRTH, AND POSITIVE FETAL ELECTROCARDIOGRAMS

WEIGHT	M.	F.	POS. EKG.	NEG. EKG.	% POS.	% NEG.
5 pounds to 7 pounds 8 ounces	11	7	13	5	72	28
7 pounds 9 ounces to 9 pounds 13 ounces	15	7	19	3	86	14
Total	26	14	32	8	80	20

Of the 5 positive breech cases with electrocardiograms, recorded 45, 28, 17, 12, and 9 days before delivery, two (seventeen and twelve days) eventually delivered as, right occiput posterior. In both of these cases, the obstetrician's diagnosis concurred with our electrocardiographic findings, although roentgenograms taken five days before delivery showed vertex presentations. The one negative breech electrocardiogram was diagnosed as a breech by means of the microphone, which located the fetal heart in the left upper quadrant, although the obstetrician's diagnosis was left occiput anterior. This patient eventually delivered a fetus in the left sacral anterior position.

The number of positive tracings was almost the same in Lead II (right arm-left leg) and Lead IV (right arm-right leg) as compared with Lead III (left arm-left leg) and Lead V (left arm-right leg). In other words, the positive tracings in all four leads were approximately the same (Table IV). This coincides with the final diagnosis of 18 right vertex positions and 18 left vertex positions. In Strassman's series, there were more left vertex positions, and, therefore, positive tracings were highest and almost the same in Leads III and V, because these leads are the most favorable for recording impulses from the fetus in the left vertex position; whereas Leads II and IV are most favorable for recording impulses from the fetus in the right vertex position. As a rule, the left vertex position occurs more frequently than the right.

The ratio of the total number of positive tracings to the total positive electrocardiograms is practically the same, irrespective of the time they were taken before delivery. This again proves our previous contention that it is not the time before delivery but the size of the fetus that determines the number of positive tracings (Table IV).

TABLE IV. RELATIONSHIP BETWEEN THE TIME BEFORE DELIVERY, NUMBER OF POSITIVE ELECTROCARDIOGRAMS, AND NUMBER OF POSITIVE TRACINGS

DAYS BEFORE DELIVERY	TOTAL POS. EKG.	POSITIVE TRACINGS					NO. POS. TRACINGS PER EKG.
		LEAD I	LEAD II	LEAD III	LEAD IV	LEAD V	
0-20	20	1	15	12	14	11	2.6
21-67	12	0	5	8	8	6	2.3
Total	32	1	20	20	22	17	2.45 Av.

TABLE II. TIME BEFORE DELIVERY FETAL ELECTROCARDIOGRAMS TAKEN AND RESULTS OBTAINED

DAYS BEFORE DELIVERY	TOTAL RESULTS												VERTEX PRESENTATION						BREECH PRESENTATION					
	TOTAL EKG.		POSITIVE		NEGATIVE		TOTAL EKG.	POSITIVE		NEGATIVE		TOTAL EKG.	POSITIVE		NEGATIVE		TOTAL EKG.	POSITIVE		NEGATIVE				
			CASES	%	CASES	%		CASES	%	CASES	%		CASES	%	CASES	%		CASES	%					
0-20	25	20	80	20	5	20	22	18	82	4	18	4	3	75	1	25	4	3	75	1	25			
21-67	15	12	80	20	3	20	12	9	75	3	15	2	2	100	0	0	2	2	100	0	0			
Total	40	32	80	20	8	20	34	27	79	7	21	6	5	83	1	17	6	5	83	1	17			

fetus, and the site of maximal intensity. The more rapid the fetal heart, the greater the intensity of its sounds.

Since the intensity of fetal heart sounds may vary, it may be difficult to differentiate the first from the second sound in the presence of systole and diastole of equal length. Under such conditions, the presence of a positive fetal electrocardiogram would help, since the R-wave of the electrocardiogram precedes the first heart sound by a few hundredths of a second (usually 0.04 sec.) (Figs. 2 and 3). A similar relationship occurs in adults with the simultaneous recording of the electrocardiogram and stethogram.

Although it has been proved that the larger the fetus, the slower the rate, the smaller the fetus, the faster the rate, it appears that the maternal rate has a definite influence over the fetal rate in spite of the size of the fetus. The difference in rate may be a helpful differential point between a large fetus and twins.²⁷

Strassman¹⁸ has shown that the impulses of the fetal heart are too weak to give in a visible way the same configuration of heart action that is found in the electrocardiogram of adults. The P- and T-waves are absent. The R-wave is the only visible part of fetal heart action during pregnancy and labor. The simultaneous recording of the fetal electrocardiogram and stethogram works both ways to prove that the R-wave is the only deflection. It precedes the first sound of the fetal heart and the first fetal heart sound follows it. The amplitude of the R-wave varies between $\frac{1}{2}$ and 2 mm., and its width between 0.02 and 0.04 sec. It is usually visible to the trained naked eye but sometimes a magnifying glass is necessary for identification.

In order to determine if a fetal electrocardiogram is positive, the following criteria are essential: (1) The R-wave must be followed throughout the entire lead; (2) it must occur at more or less regular intervals; (3) the interval must correspond in length to the distance between each fetal heart beat as recorded on the stethogram; and (4) the exact fetal heart rate as determined by the distance between two fetal waves must correspond to the rate as determined by the fetal stethogram. In determining the fetal heart rate, the same method is used as in adult electrocardiography.

Since in vertex presentation, the fetal heart is upside down in relation to the maternal heart, the fetal R-wave appears as a negative wave deflected below the isoelectric line, and is sometimes followed by a very short positive wave (Figs. 3 and 4). In breech presentation the opposite takes place, a positive R-wave is followed at times by a short negative wave (Figs. 5 and 6). There was no difficulty in studying either the positive or negative waves, because in all tracings, fetal waves are better detected on the isoelectric line than on any of the maternal waves. When the fetal waves coincide with the maternal QRS complex, they are never visible. When they coincide with the maternal P- and T-waves, they are hardly visible.

We wish to detail Case 36, a positive breech electrocardiogram, as one of the most unique fetal tracings ever recorded (Fig. 6). There is no fetal electrocardiogram on record in which the waves are recorded in Lead I. Theoretically, it is assumed that the tracing in Lead I is positive only in cases of transverse

Although twins were suspected by the obstetrician in 2 cases, we were able to disprove this by the fetal electrocardiogram and stethogram. Follow-up verified our results. Unfortunately no opportunity of recording multiple pregnancies has been presented. Bell has the only positive tracing of twins on record.

DISCUSSION

The association of irregularities of rhythm, murmurs of the fetal heart, and pronounced slowing of the rate may in occasional instances be due to congenital heart disease, and the diagnosis can be made before delivery.²⁴ None of our cases of sinus arrhythmia or normal rhythm showed any stethographic evidence of congenital heart disease. All hearts examined after birth were normal. Sampson, McCalla, and Kerr,²⁵ working on phonocardiography of the human fetus, reported 31 cases of fetal cardiac irregularities, but in only one instance was there a congenital heart lesion. Sinus arrhythmia is a common finding in fetal hearts. It has no clinical significance, and is explained on the basis of a myogenic or a neurogenic origin, due to a relatively unstable pacemaker.

Of the 13 cases of uterine souffle recorded, 6 were on the left and 7 on the right side. This coincides with the equal number of right and left vertex positions in our series. The uterine souffle is a humming, blowing, rushing, sibilant, or even musical sound synchronous with the maternal heart. It originates in the large vessels, arteries and veins in the sides of the uterus. It is heard best on the lower left side of the uterus, but may be heard on the right side, anteriorly on both sides, and occasionally all over the abdomen. It may be loud, drowning the fetal heart tones as demonstrated in 4 of our cases, or soft, hardly audible, and even absent in some cases (10 per cent).²⁶ It may be heard at one time and be absent in the same place later. Some of our tracings show the above characteristics. It is usually systolic but may be both systolic and diastolic. It is found whether the fetus is dead or alive, and is not a diagnostic sign of pregnancy because it is heard over rapidly growing tumors.

Heart sounds consist of mixtures of frequencies or noises. They are never pure musical notes having single frequencies. The dominant frequencies of the various sounds tend to remain the same in each individual, regardless of the cardiac rate or of the sites at which the microphone is placed. The frequency composition^{29, 30} of fetal heart sounds is similar to that of adult heart sounds. The amount of sound energy is, however, considerably smaller than for adult hearts. Since in certain cases, the ear is incapable of detecting fetal heart sounds, it is obvious that obstetric auscultation requires acuity of hearing at low frequencies. The absolute and relative intensities of sounds change greatly when the microphone is moved from one place to another, and when the heart rate changes.¹⁰ This is demonstrated by placing the microphone at the apex or base of the adult heart. The intensity of fetal heart sounds depends upon the site at which the microphone is placed, as well as upon maternal and fetal conditions which may interfere with the transmission of sound. These conditions include thickness of the abdominal wall, change in position and movements of the

heart rate that not only approximates the maternal rate, but even becomes slower than the maternal rate. In Lead I, the maternal rate is 125 (sinus tachycardia), and the fetal rate is 94. At the beginning of Lead II, the maternal rate is 150 (marked sinus tachycardia), and the fetal waves are not detected, due to the marked sinus tachycardia. As the maternal rate slows down in this lead to 83, the fetal waves are detected and the fetal rate is still 94 beats per minute. At the beginning of Lead IV, the maternal rate is now 65 and the fetal rate slows down to 83. Toward the end of Lead IV, the maternal rate becomes 75 and the fetal rate still remains at 83. The above variations in rate were temporary, because the fetal rate at birth was 140. It seems that the mechanism involved in the above rate changes affected not only the mother but also the fetus. Whether the fetal heart rate was chiefly influenced by the maternal rate and vice versa, or both were separately affected, is difficult to state. One can simply imply that the condition was undoubtedly a temporary sympathetic-vagal disturbance affect-

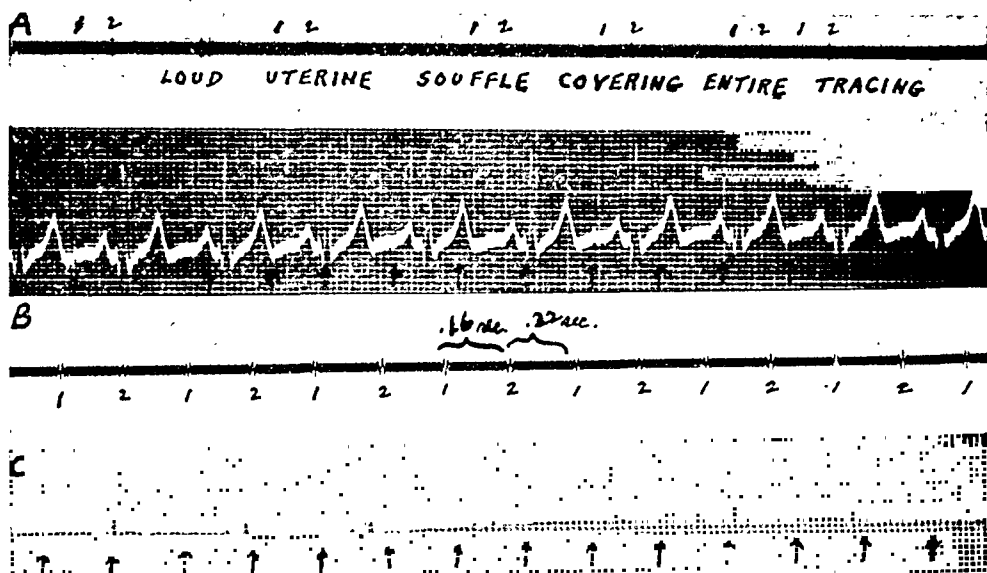


Fig. 5.—Simultaneous recording of fetal electrocardiogram and stethogram. *A*, fetal sounds are covered by a loud uterine souffle, making it difficult to detect and differentiate the sounds. Second sound is louder. Fetal waves help to distinguish the sounds and vice versa. Arrows indicate upright or positive waves (breech presentation). Film speed is 25 mm. *B*, fetal heart sounds with film speed of 50 mm. Note variations in intensity of the sounds. *C*, same case as *B*, except that the fetal electrocardiogram has a film speed of 25 mm. Arrows indicate inverted or negative fetal waves (vertex presentation).

ing both mother and fetus. In the fetus, it was a sinus bradycardia or possibly a temporary heart block, and in the mother it was a sinus tachycardia. There is no doubt of the uniqueness of this case from every standpoint. Although the baby was discharged as normal at birth, a follow-up study will be made.

Conditions sometimes arise (infections, hyperthyroidism, etc.) in which the maternal rate becomes rapid, making it difficult to differentiate maternal from fetal rate. In such instances, Lönne³² suggests the simple procedure of taking a deep breath after quiet breathing, and holding it. Thus one approaches the physiologic rate, whereas the fetal rate is not disturbed. In our unique case, it would have been difficult to differentiate maternal from fetal rate without the use of the fetal electrocardiogram.

In evaluating the cause of our 8 negative fetal electrocardiograms, several factors are involved. Two cases (twenty-seven and twelve days

position of the fetus, because in longitudinal positions (vertex or breech presentation), the axis of the fetal heart is vertical, and, therefore, the isoelectric zones are horizontal and parallel to Lead I (right arm-left arm). In this case of right sacral anterior, there are positive or upright fetal waves in Leads I, II, and IV.

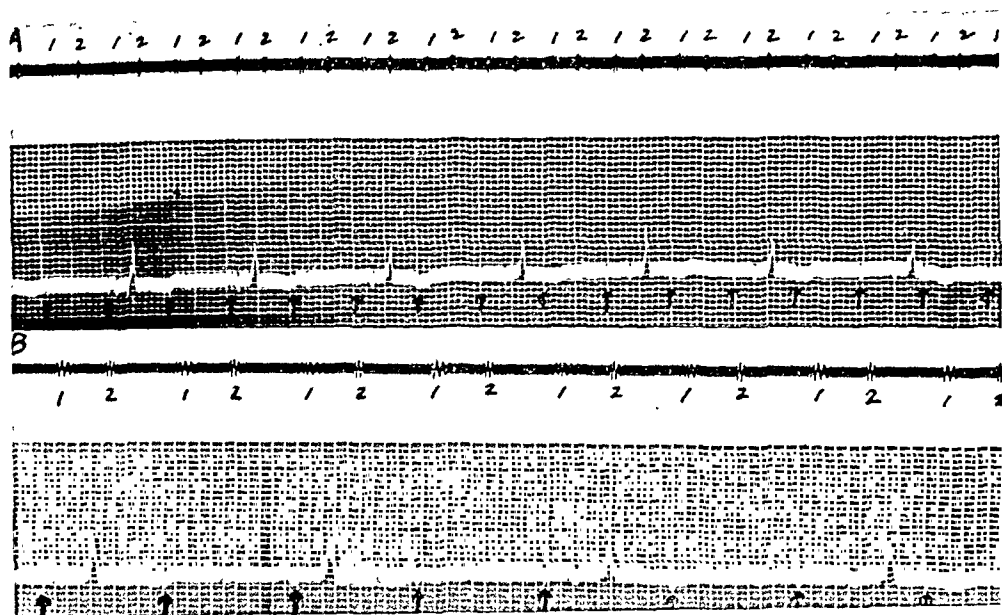


Fig. 3.—Simultaneous recording of fetal heart sounds and fetal electrocardiogram. A, speed of film is 25 mm. per second. Note definite relationship between the first sound and the R-wave of the fetal electrocardiogram. Arrows indicate inverted or negative R-waves (vertex presentation). Second sound is louder than first sound. B, same as A, except that speed of film is 50 mm. per second.

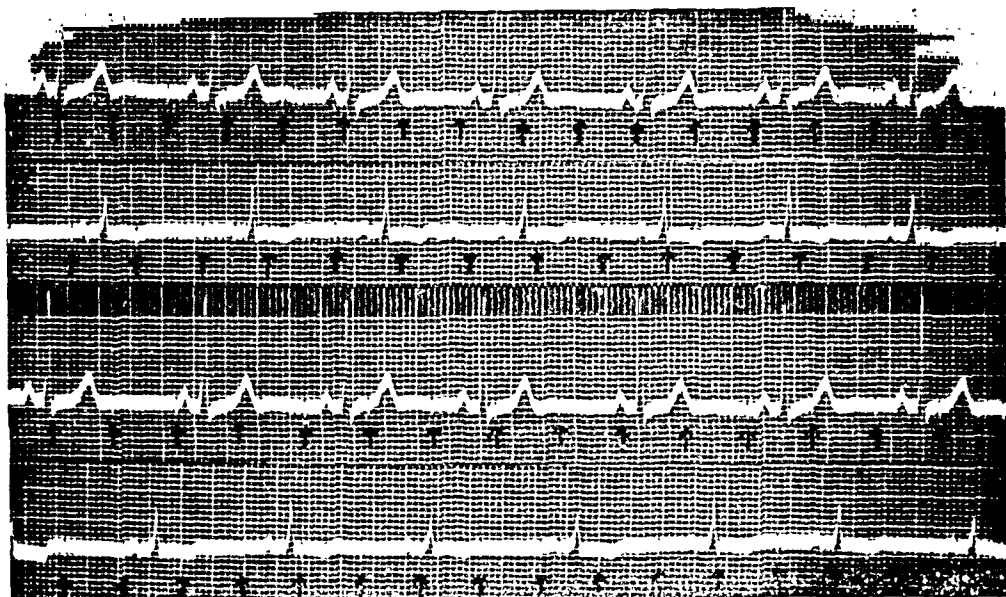


Fig. 4.—Fetal electrocardiogram, Leads II, III, IV, and V. Arrows indicate fetal waves (R-waves) which are inverted or negative, indicating vertex presentation. Note that fetal waves are excellent in spite of fuzzy tracing.

The only reason we can advance for the positive Lead I, is that the fetus was in an oblique position, with the axis of the fetal heart transversely and parallel to Lead I. The electrocardiographic diagnosis is a transverse heart and a breech presentation. Another interesting feature of this case is the presence of a fetal

TABLE V. RELATIONSHIP BETWEEN LOCATION OF FETAL HEART, OBSTETRICIAN'S DIAGNOSIS, AND FINAL DIAGNOSIS ON DELIVERY

DAYS BEFORE DELIVERY	POSITIVE EKG.		LOCATION OF F.H. BY MICROPH.				OBST. DIAGNOSIS				FINAL DIAGNOSIS			
	VERTEX	BREECH	R.L.Q.	L.L.Q.	R.U.Q.	L.U.Q.	R.O.	L.O.	R.S.	L.S.	R.O.	L.O.	R.S.	L.S.
0-20	18	3	11	11	1	2	8	15	1	1	11	12	1	1
21-67	9	2	7	7	1	0	12	3	0	0	7	6	2	0
Total	27	5	18	18	2	2	20	18	1	1	18	18	3	1

NOTE: Two positive breech presentations, by fetal electrocardiogram, delivered as right occipitoposterior position, and the one negative breech presentation delivered as a left sacral anterior position. This accounts for the discrepancy between the number of positive breech electrocardiograms and the final diagnosis.

before delivery) gave excellent tracings but both showed a maternal sinus tachycardia and one a fetal sinus arrhythmia. Four cases (twenty-one, eleven, five, and two days before delivery) gave excellent tracings, but the size of the fetus was in the lower weight group. In the last 2 cases (twenty-five and eight days before delivery), the patients were very nervous, and the tracings showed evidence of interference due to muscle tremor. One of these cases was also in the lower weight group.

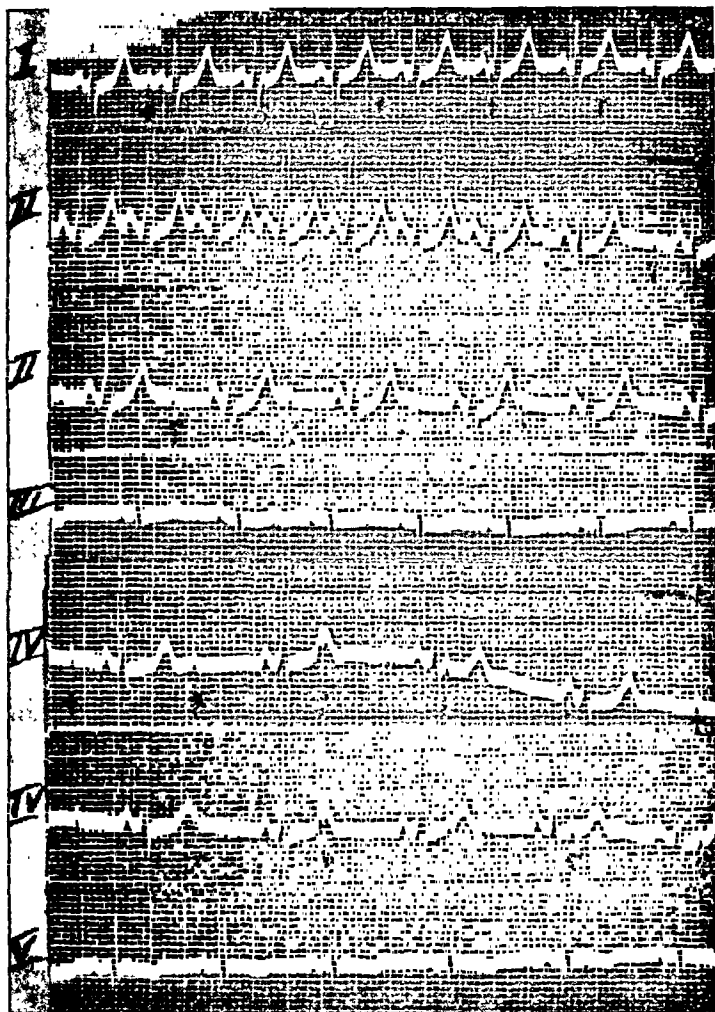


Fig. 6.—Fetal electrocardiogram, Leads I, II, IV. Arrows indicate upright or positive waves (breech presentation). For full description see text.

Of the 8 negative cases, 5 were in the lower weight group. In addition to the weight of the fetus, nervous patients, maternal sinus tachycardia, and possibly fetal sinus arrhythmia may be factors in the causation of negative electrocardiograms.

CONCLUSIONS

It is interesting to note that the diagnosis of position, by location of the fetal heart by means of the microphone, is more accurate than the obstetrician's diagnosis (by ordinary methods), when compared with the final diagnosis on delivery. This comparison is made with due con-

fortunate in recording the only positive fetal waves on record in Lead I in a breech presentation. We advanced the reason for this paradox as due to the transverse position of the fetal heart in an oblique breech presentation.

The fetal electrocardiogram is indispensable in differentiating between first and second heart sounds, in the presence of equal systolic and diastolic phases caused by fetal tachycardia.

Its value also lies in the fact that a combined tracing of the maternal and fetal electrocardiograms can be studied, and used as a permanent record for medicolegal or other purposes.

There is no doubt of its value in twin pregnancies as shown by Bell's case, in which both waves were upright, proving the presence of two breech presentations. It is certainly of great help to the obstetrician to know in advance the presentation of twins so that he can plan his method of delivery.

We have enumerated the results and value of each method separately. By combining both methods, the positive results of our procedure are certainly enhanced, and the most complete records for study are obtained. We do not expect our method to replace the obstetrician's routine periodic examination, but to be used concomitantly if possible and as a consultation service if necessary, because we feel that the technique is simple, the time consumed in the process insignificant, and the results of indubitable value.

We hope that our combined method will stimulate further study along these lines.

SUMMARY

Forty gravidas were studied routinely in the last two months of pregnancy, to determine the diagnostic significance of the fetal electrocardiogram and the fetal stethogram, separately and simultaneously, in evaluating the presence of a viable fetus. The individual value of each method was enhanced by the combined study.

The fetal stethogram was positive in 100 per cent of the cases, the fetal electrocardiogram in 80 per cent.

The stethogram is helpful in studying the rate, rhythm, and regularity of fetal heart sounds, the systolic and diastolic phases, murmurs, the uterine souffle, and fetal movements. The intensity of fetal heart sounds depends upon the site at which the microphone is applied, and upon maternal and fetal conditions. In most cases the second sound is louder than the first. As a rule, diastole is longer than systole, but in the presence of fetal tachycardia they may become equal.

The electrocardiogram is valuable in the presence of positive tracings. The absolute diagnosis of fetal presentation is made by the fetal electrocardiogram. If the waves are negative, a vertex presentation is present; if positive a breech presentation is present. In the presence of an equal systolic and diastolic phase, the first sound is recognized by its relationship to the R-wave of the fetal electrocardiogram.

sideration to the possible change of position before delivery (Table V). The most accurate method of detecting presentation is by means of a positive fetal electrocardiogram.

It is obvious, from our results, that the study of the fetal heart by the fetal electrocardiogram and stethogram, either separately or simultaneously, is the only method available at present for an accurate estimation of fetal life.

One cannot always depend on ordinary hearing for accurate results,³⁰ as well as one cannot at times depend on amplified hearing. But a recorded tracing of sounds can never fail, provided there is something to record. A contracting fetal heart muscle will always produce sounds which can be recorded by the stethograph or any similar instrument.²⁸ By the same token, fetal movements due to muscular contraction produce sounds which can be definitely recorded.

The method of sound recording gives us further information concerning the fetal heart. The first and second sounds, and the systolic and diastolic phases can be accurately studied. The presence of other sounds (third and auricular sounds), adventitious sounds (uterine souffle), cardiac murmurs (congenital heart disease), and irregularities of rate and rhythm (sinus arrhythmia, sinus tachycardia, sinus bradycardia, and congenital heart block), of the fetal heart beat can be visualized. The exact location of the fetal heart can be determined by the microphonic attachment. And finally, our series shows 100 per cent accurate diagnosis of fetal life by the stethogram and verified by 40 live babies at birth. Although there were no twins in our series, it would be interesting to study stethographic records under such conditions.

We believe that the technique for the detection of the fetal electrocardiogram has been well perfected by Strassman.^{18, 19} The occurrence of a negative fetal electrocardiogram does not depend as much on the technique used as on the presence of other factors. We have conclusively proved in our series that the size of the fetus is an important factor, irrespective of the time before delivery, provided the electrocardiogram is taken within the last two months of pregnancy. We have suggested that maternal tachycardia and perhaps fetal sinus arrhythmia may be factors. A nervous patient will cause fuzziness of the tracing due to muscle tremor, and so become an important factor in a negative fetal electrocardiogram. Whatever the cause, we feel certain that the technique is not at fault.

The positive fetal electrocardiogram gives accurate information concerning fetal life as well as becoming an accurate aid in the diagnosis of fetal presentation. The mere presence of a positive tracing means a live fetus, whereas its absence does not signify fetal death, if certain factors mentioned above are present. If these factors are absent and the tracing is excellent, then fetal death should be considered and, of course, verified by the stethogram. The presence of a negative fetal wave means the presence of a vertex presentation at the time the tracing is taken. The presence of a positive fetal wave signifies the presence of a breech presentation at the time the tracing is taken. We were

HYPERTHYROIDISM AT THE MENOPAUSE

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IN STATES of ill health, the female patient at the climacteric presents a diagnostic problem to the internist, as well as to the surgeon. The question is, are we dealing with an organic disease or simply with a manifestation of the beginning menopause? The symptoms of the menopause are so protean in nature as to mimic almost any type of organic disease, e.g., cardiac, gastrointestinal, pulmonary, cerebral, pelvic, to mention but a few.

In this presentation we wish to stress the close relationship between menopause and the thyroid gland.

Menopause and hyperthyroidism have many leading symptoms in common. They are: increased sweating, irritability and nervousness, palpitation, increased sense of heat, etc. To differentiate the hyperthyroid symptoms from those of menopause may become very perplexing.

Claiborne¹ in discussing the differential diagnosis of borderline hyperthyroidism has recently commented on this subject. He states, "During the time of the menopause many women have symptoms which are in part suggestive of hyperthyroidism. These patients begin to note a feeling of warmth, perspire readily, are emotionally unstable, cry easily, are irritable, complain of palpitation, and so forth. The decrease in menstruation may confuse the issue: is it a symptom of hyperthyroidism or beginning of the menopause? There is usually no weight loss and no appetite change. An elevated basal metabolic rate is frequently obtained; but repetition gives a drop to normal." It has been our experience that the majority of women at the menopause show a variable basal metabolic rate. According to some investigators, there is a slight fall in the basal metabolism in artificial menopause induced by surgery or roentgen ray castration.²

The physiologic relationship between the thyroid gland and the reproductive function is vast and intriguing. Comparatively little factual knowledge on the subject is on hand.

It is a well-recognized clinical fact that thyroid diseases occur more commonly in women than in men; and that the thyroid gland is enlarged at puberty, pregnancy, lactation, and the menopause. The physiologic basis for these clinical observations may be gleaned from the experimental work on the effect of the pituitary on the ovary and the thyroid.

EXPERIMENTAL WORK

Castration in animals increases not only the production of prolactin A but also of the thyrotropic factor of the anterior pituitary lobe.³ The overproduction of the thyrotropic substances result in hyperplasia of the parenchyma of the thyroid

The factors involved in negative electrocardiograms are, a nervous mother, a small fetus, maternal tachycardia, and possibly fetal sinus arrhythmia.

The combined tracings give permanent records of documental value. The maternal electrocardiogram is also recorded.

The use of fetal electrocardiography and fetal stethography for routine and consultation purposes is recommended because of the simple procedure involved and the ease with which tracings can be interpreted.

A case of breech presentation with positive tracing in Lead I, and variations in maternal and fetal rate is discussed.

We wish to express our thanks to the Department of Obstetrics for permission to study their cases. We wish to express our appreciation to Dr. Anthony R. Colonna for his technical assistance.

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Petersen, E.: The Results of Operations on the Sympathetic Nervous System for Benign Gynecologic Conditions, Acta. obst. et gynec. Scandinav. 20: 1, 1940.

The author analyzes his remote results with pelvic sympathectomy performed for benign gynecologic conditions. Of the 7 patients operated upon for dysmenorrhea, 4 were cured, one was given partial relief and 2 had no relief. In 5 cases of chronic parametritis, 2 patients had complete relief, 2 only partial relief, and 1 observed no change. In 53 patients where the operations were performed for microcystic degeneration of the ovaries, the results were not striking but pain was reduced somewhat more effectively than a control group of 42 patients where no operation was performed.

J. P. GREENHILL.

exophthalmus. The right lobe of the thyroid was the seat of a nodule, the size of an English walnut. The examination of the heart showed no heart disease. The lungs were clear. There was some tenseness in the right lower quadrant of the abdominal wall. The hair distribution was essentially feminine in type with scant axillary hair. The palms of the hands were moist and cold. The fingers showed no tremor. On June 13, 1935, the basal metabolic rate was minus 9 and the blood cholesterol 240 mg. per 100 c.c. Patient was given $\frac{1}{4}$ gr. of desiccated thyroid three times daily for two weeks. The pulse rate increased to 128, and the temperature was 99.4° F. The thyroid medication was omitted; however, the pulse rate remained elevated at about 120 per minute for a period of four weeks; during this time she complained mostly of belching. Because of the increased pulse rate and elevated temperature, pulmonary pathology was considered. Physical examination of the chest including roentgenographic studies were negative. No apparent cause for the tachycardia could be found, except for the presence of the adenoma of the thyroid gland. Because of a similar previous experience¹² in which thyroidectomy brought about complete relief from tachycardia and cardiac arrhythmia, the patient was admitted to Temple University Hospital for thyroidectomy. The basal metabolic rate at this time was plus 9 per cent. The cardiologist's report was mild myocardial degeneration secondary to arteriosclerosis and possibly thyrotoxicosis. After proper preparations with Lugol's solution and rest, the patient was operated upon on Sept. 30, 1935. At operation, an adenoma of the right thyroid lobe, the size of a plum, was removed. The left lobe was not disturbed. The microscopic examination of the removed tissue showed numerous large focal regions of fibrous tissue. The thyroid gland itself was inactive. The glands were small and exhibited a moderate amount of mucoid degeneration. Patient was discharged from the hospital on Oct. 7, 1935. For the following two months her pulse rate averaged 88 per minute. The basal metabolic rate was minus 6 per cent, the blood cholesterol 230 mg. per 100 c.c. of blood. On Dec. 17, 1935, she was seen in the Endocrine Clinic with a pulse rate at rest of 100 per minute. Despite sedatives, it continued to vary between 100 and 112 per minute. The patient did not return to our clinic for one year. On Feb. 3, 1937, she came to the clinic complaining of belching, weakness, hot flushes, and vertigo. Her pulse rate was 100 per minute. Her menses were becoming irregular in addition to being scanty. On Feb. 5, 1937, she was started on 2000 rat units of progynon twice a week. After several weeks' treatment, her symptoms began to improve. On April 30, 1937, her pulse rate was 84 per minute, and she weighed 112 pounds (ten pounds more than at first visit) and she had no complaints. Progynon was continued for six months at less frequent intervals than in the beginning of the treatment. When she was last seen at our clinic on Dec. 29, 1937, her pulse rate averaged 84 per minute. Blood pressure was 126/72. Weight 111½ pounds. She had been free of her symptoms and had been able to attend to her household duties.

Comment.—This patient was at the menopausal age (45 years); she had been noting the change in amount of her menstrual flow; she had symptoms of dyspepsia. She also complained of nervousness and insomnia. Her pulse rate was persistently elevated. All of these symptoms could have been due to the oncoming climacteric. Because there were no clear-cut signs of the menopause, such as hot flushes, sweats, vertigo, amenorrhea, this phase of her illness was probably minimized. It is interesting to note that the basal metabolic rate was not abnormal before or after the operation. It is apparent that the primary purpose of the operation, i.e., the relief of the so-called mild thyrotoxic symptoms had not been accomplished. The vasomotor symptoms were not relieved until estrogen therapy was resorted to. A subtotal thyroidectomy in cases of this type may lead to postoperative myxedema as illustrated by the following patient.

CASE 2.—R. H., aged 42 years, white, married, came to the Endocrine Clinic of the Temple University Hospital on Jan. 27, 1937, because of the presence of a "goiter." She had noticed the goiter one and one-half years previously. It had increased slightly in size since then. In addition she complained of nervousness, irritability, easy fatigability, and free perspiration. The menstrual flow was

gland with increased vascularization and reduction in the colloid, a histologic picture which characterizes hyperthyroidism.⁴ Grumbrecht⁵ succeeded in obtaining similar histologic changes in thyroid glands of rabbits when injected with urine from women at the climacteric. It is interesting to note that the thyrotropic substance is found in small quantities in the urine in premature or late menopause, or at the time of comparatively few vasomotor symptoms. On the other hand, the level of thyrotropic substance in the urine is at its peak when the vasomotor symptoms are at their height.⁵

The experimental work of Sherwood and his associates⁶ is cogent in this connection. They found a definite decrease in the basal metabolism of adult ovariectomized rats following the administration of estrogen. Estrogen likewise proved effective in reducing the basal metabolic rate of experimental hyperthyroid animals that were not ovariectomized.⁷

From these observations and those of Gessler,⁸ the thought comes to mind that perhaps the use of the female sex hormone (estrogen) in thyrotoxicosis at the menopause may prove beneficial.

THE CLINICAL PROBLEM

The problem involved in the diagnosis of the menopause when a nodular goiter is present is far from simple. The emotional instability, sweats, flushes, and the vasomotor symptoms of menopause may mimic those of hyperthyroidism. Needless thyroid surgery is frequently being performed in this group of patients. A recent follow-up study of 100 patients who were advised to have a thyroidectomy for hyperthyroidism revealed that in 15 patients the diagnosis of hyperthyroidism had to be reversed in favor of the menopause.⁹ The basal metabolic rate determination cannot always be depended upon for differential diagnosis. Due to the patient's state of apprehension, it is difficult or impossible for her to relax; in the effort to abolish movements, she increases energy expenditure which may cause an increase in metabolic rate. A fleeting emotional upset or a wave of nausea may also increase the metabolic rate.¹⁰

Since estrogenic therapy is known to control the vasomotor phenomena of menopause, this form of therapy may be employed in the borderline patient before thyroidectomy is decided upon. Recently Davis¹¹ reported favorable results in the relief of menopausal symptoms in 93 of 100 women by the oral use of stilbestrol. This oral method of administration would appear to offer an additional practical means of differentiating the borderline hyperthyroid patient from menopause.

The following six patients observed at the Temple University Hospital are illustrative of the points under the present discussion.

CASE 1.—E. H., aged 45 years, white, single, was first seen in the Endocrine Clinic of Temple University Hospital on June 6, 1935. Her chief complaint was "nervous indigestion and insomnia." The patient had been suffering with dyspepsia for many years. She had been studied in the gastric clinic; however, no definite etiology had been ascertained. She had lost 10 pounds in the past year. Her menses started at the age of 14 years, were regular, every twenty-four to twenty-six days, lasted three to four days. No pain. Lately they were becoming more scant. Her past medical history revealed that she had an attack of "indigestion" two years ago for which she was confined to bed for six weeks.

Examination showed a thin, middle-aged, white female with a quizzical expression (due probably to her difficulty in hearing); weight was 102½ pounds, height 61½ inches. Temperature was 98° F., pulse 80, respiration 20, blood pressure 140/90. The skin was dry and showed dermatographia. The eyes showed no

questioned about the sensation of tightness in her neck, she volunteered the information that she still feels it and sometimes more than before the operation.

Comments.—Here we have another patient at the climacteric with a multitude of bizarre symptoms suggestive of adenoma of the thyroid gland, gall bladder disease, pernicious anemia, and menopause. Such patients are often easier to pigeonhole diagnostically after failure in therapy than before treatment. The original symptoms of scanty menses, nervousness, vasomotor signs, etc., could have been due to early climacteric. The gastrointestinal symptoms were those of hypochlorhydric hypochromic anemia of menopause. It is unfortunate that the patient fixed her attention on her "goiter" and "tightness" in the neck. The fixation was so marked as to lead her medical attendants to believe that the thyroid was conditioning her symptoms to the exclusion of a physiologic process of menopause. There is a strong possibility that the thyroid which was removed was already hypofunctioning, and the adenoma had undergone cystic degeneration. The surgical removal of the thyroid not only failed to cure the patient's symptoms but aggravated her condition by bringing about a myxedematous state.

On the basis of the experience with these two cases, we treated the following two patients' similar symptoms by medical measures rather than by surgical intervention. The progress of these cases is as follows:

CASE 3.—A. McN., aged 45 years, white, married, was referred to the Endocrine Clinic of Temple University Hospital on Sept. 14, 1937, for a basal metabolic rate determination, and physical examination prior to an operation for a toxic adenoma of the thyroid gland. The essential findings in our clinic were as follows: A history of easy fatigability, excessive sweating, and frequent attacks of palpitation. There had been no weight loss. There had been an artificial menopause at the age of 30 years, following hysterectomy for fibroids, but no vasomotor symptoms developed until four years ago. Past medical history was irrelevant. Examination revealed a middle-aged woman, weighing 149 pounds and of average build. The face was flushed; the skin of body was moist and of normal texture. The neck showed a small nodule the size of an olive in the isthmus of the thyroid gland. The palms of the hands were moist and the extended fingers showed a tremor. The heart rate was slightly elevated, apical rate 96, no murmurs and no arrhythmia. The lungs were clear. The other findings were within normal limits. A basal metabolic rate on Sept. 17, 1937, was plus 37 per cent. Despite the elevated basal metabolic rate, she was considered to suffer from menopausal symptoms. She was given one international unit of progesterin, three times a week. After six injections, she stated that she was less nervous, felt much improved, and her pulse rate declined to 80 per minute. A basal metabolic rate determination on Oct. 21, 1937, was minus 6 per cent. Unfortunately a blood cholesterol was not determined due to clotting of the blood specimen in the tube. The patient received 16 more injections of progesterin. She was free of symptoms and when we last heard from her, she was reported to be in good physical condition and not taking any medication.

Comment.—This case discloses a few pertinent points. First, the elevated basal metabolic rate (plus 37) may have been due largely to the patient's fear of surgery. DuBois has mentioned this as an important factor in false readings of basal metabolic rates. It is imprudent to say to the patient, "We'll do a basal metabolic rate to see whether your thyroid will have to be removed surgically." Second, the drop in basal metabolic rate from plus 37 to minus 6 may, therefore, be due to improvement of vasomotor symptoms. Be that as it may, the relief of the patient's symptoms following the injections of progesterin is highly suggestive that we were not dealing with a true toxic goiter, but rather with vasomotor phenomena of menopause.

CASE 4.—J. I., aged 43 years, white, married, was referred to the Endocrine Clinic of Temple University Hospital by her family doctor with a note that she had had for many years a simple goiter, asymptomatic. Two months ago she had bronchopneumonia. During the course of that disease symptoms of an exophthalmic goiter became manifest. The findings at our clinic were as follows: Patient noticed a "lumpy swelling" over anterior region of neck about three years ago. This lump was stationery in size until September, 1938, at which time she devel-

becoming scant. Her family physician diagnosed her condition as that of toxic goiter. X-ray treatment to the thyroid gland was given for six months. The menstrual flow increased to a more normal amount, but the vasomotor symptoms were unrelieved. When she was told by her doctor that the goiter would have to be removed surgically, she left his care and went to a chiropractor, who treated her for one year with no improvement. At no time had a basal metabolic rate been determined. When she came to the Endocrine Clinic of Temple University Hospital, she still had all of the above symptoms. Her appetite was good and there had been little change in her weight. She also complained of frequent indigestion, epigastric pressure and distention. The physical examination revealed an apprehensive, middle-aged white female, whose face was quite flushed. She was of normal build; her weight was 149 pounds. Temperature, pulse, respiration were 98.2°, 80, 20, respectively. Blood pressure 110/88. There were no eye signs of hyperthyroidism. The pupils were equal and reacted normally to light and accommodation. The thyroid gland was palpable, symmetrically larger than normal, containing a nodule, the size of a walnut in the left lobe. The skin of the upper chest showed the collar flush, characteristic of vasomotor instability. The heart and lungs were essentially normal. There was slight epigastric tenderness on palpation. Other physical findings were essentially normal. Her basal metabolic rate on Jan. 30, 1937, was minus 12 per cent. Our impression was that the patient had a nontoxic goiter and gall bladder disease. She was referred for gastrointestinal studies. Gastric analysis revealed hypoacidity Grade II; gastroscopic examination showed evidence of an atrophic gastritis. X-rays of the gastrointestinal and biliary tracts were negative. The urinalysis was normal, and the blood count was as follows: hemoglobin 8.5 Gm., or 53.5 per cent; red blood cells, 3,950,000; white blood cells, 8,950; color index, 0.69; polymorphonuclears 59 per cent, lymphocytes 37 per cent, and monocytes 4 per cent. The red blood cells showed anisocytosis, poikilocytosis, and achromia. This type of anemia is not infrequently seen at the menopause. The Wassermann test of the blood was negative. The patient was treated for the next three months with iron sulfate, hydrochloric acid, sedatives, and antispasmodics. The blood picture improved considerably, but the gastrointestinal and vasomotor symptoms remained unchanged. In addition, she developed a sensation of tightness in the neck that became quite annoying. The basal metabolic rate at this time was plus 12 per cent. A surgical opinion was in favor of thyroidectomy. On Aug. 11, 1937, a subtotal thyroidectomy was done. The surgeon noted that "the thyroid gland was vascular, hemostasis difficult, vessels sclerosed from previous irradiation." The pathologic report showed that the acini varied greatly in size and shape. All were fairly well filled with colloid and lined by low cuboidal epithelium. There were large areas of the stroma which showed a marked degree of hyalinization. In one section there was considerable hemorrhage. *Diagnosis:* Cystadenoma of thyroid.

The patient made an uneventful recovery and was discharged from the hospital in good condition. Two months after the operation, on Oct. 11, 1937, she came to the Endocrine Clinic complaining of feeling weak and tired. She had occasional swelling of her feet and puffiness about lower eyelids. The pulse rate was 78 per minute. The basal metabolic rate was minus 39 per cent. She was placed on $\frac{1}{2}$ gr. of desiccated thyroid, three times daily, and the dosage was gradually increased to 3 gr. daily. The edema subsided but the vasomotor symptoms persisted. Because of this and scanty menses, she was started on 2,000 rat units of progynon, twice a week. After several weeks she showed improvement. Her flushes, sweating, nervousness, fatigue, all decreased markedly. It is interesting to note that with the rise of the basal metabolic rate, the vasomotor symptoms would increase. On omission of thyroid therapy and administration of progynon, the vasomotor symptoms would subside; however, the basal metabolic rate would decline rapidly and the symptoms of myxedema would become manifest. After the trial and error method, the patient was given $\frac{1}{4}$ gr. of desiccated thyroid, three times daily and 2,000 rat units of estrogen, once weekly; 3 gr. of iron sulfate, three times daily and 15 minims of hydrochloric acid with each meal. On this regimen she remained free of symptoms and was well maintained. It is worthy of note that when

menced at the age of 13 years, was always regular and of normal flow; in the past seven months, the intervals were less frequent and the flow less scant.

On admission to the Hospital, the patient appeared underweight, very alert, and quite cooperative. There was capillary flushing over neck and upper chest. The thyroid gland was enlarged; the right lobe and isthmus contained firm nodules; the left lobe was diffusely enlarged. The outstretched fingers of both hands showed no tremor. The lungs were clear. The heart was markedly enlarged to the left. There was a diastolic murmur audible at the apex and systolic and diastolic murmur were heard at the base. The pulse was 90 per minute, quickly receding; the blood pressure was 175 systolic and 95 diastolic. The liver and spleen were not palpable. The deep tendon reflexes were present and active; there was no clonus and no Babinski. Romberg was negative. There was no weakness of the quadriceps femoris muscle group.

Laboratory Findings.—Basal metabolic rate plus 32 and plus 37 (after five days of Lugol's solution). Blood Wassermann reaction was four-plus. Spinal fluid was negative for Wassermann test and colloidal gold. Urea nitrogen was 14 mg. per 100 c.c. of blood, and urea clearance 56 per cent of normal, first hour and 72 per cent second hour. Blood count: hemoglobin, 10 Gm.; red blood cells, 4,000,000; white blood cells, 8,300; polymorphonuclears, 83 per cent; small lymphocytes, 16 per cent; large lymphocytes, 1 per cent. X-ray of the chest showed enlarged heart, and widening of root of aorta. Both exhibited abnormal and vigorous pulsations, and the arch of the aorta was not aneurysmal. The lung fields were clear; there was old adhesive pleurisy at both costodiaphragmatic angles. Patient was seen by various men of the staff of Temple University Hospital, and it was the general consensus of opinion that she should not be operated upon, as she probably did not suffer from thyrotoxicosis. She was given antisyphilitic treatment; however, she continued to complain of nausea, hot flashes, vertigo, and palpitation. She developed menorrhagia for one month. It was the opinion of the gynecologic clinic that the patient was undergoing the menopause. After cessation of bleeding she was given 2,000 rat units of estrogen, twice weekly for a period of several months. She was last seen in the medical clinic on July 8, 1940; patient had improved considerably, having an occasional hot flush, but no nausea, no palpitation, and no irritability. She is still attending the clinic for antisyphilitic treatment.

Comment.—The evaluation of the clinical signs and laboratory findings in this patient presented some difficulty. That she had syphilitic heart disease and hypertension was quite evident. It is true that in hypertension there may be loss of weight and elevated basal metabolic rate. Wohl and Robertson¹³ found an elevated basal metabolic rate of plus 27 per cent in hypertension. However, the presence of nodules in the right lobe of the thyroid and enlargement of the left lobe suggested the possibility of thyrotoxicosis. The failure of iodine administration to relieve the clinical symptoms and to reduce the basal metabolic rate spoke against the existence of thyrotoxicosis. The symptoms of vasomotor instability were doubtless due to menopause. Similar symptoms, however, may be obtained in hypertension. However, upon administration of estrogen, the vasomotor symptoms cleared in spite of the fact that the blood pressure remained high.

CASE 6.—Mrs. M. F., aged 41 years, was admitted to the hospital on May 13, 1933, with complaints of nervousness, flushing, and extreme palpitation. She had been treated for nervousness by a physician about three years prior to admission, although she had an enlarged thyroid gland at that time. Her symptoms failed to respond to treatment. In November, 1932, she had a tonsillectomy, followed by vaccine therapy. Shortly thereafter, her nervousness increased and she developed palpitation, easy fatigability, and flushing. The menstrual history was essentially normal and regular; however in the past four months the flow was scant. Physical examination revealed a well-nourished white female, who was quite apprehensive. The eyes "had a stare" with suggestion of a positive von Graefe sign. The thyroid gland was enlarged and rather firm. There was marked pulsation of the vessels of the neck. The heart was enlarged especially to the left; first sound, forcible and loud. There was a reduplication of the second sound. Blood pressure was 160/70, and pulse 110. *Abdomen:* No intra-abdominal masses were felt. *Extremities:*

oped bronchopneumonia. Soon after this the mass increased in size. She tired easily; had palpitation and dyspnea on exertion. Menstrual history: onset at 11 years, regular until the age of 20 years; after this the menses became scanty, lasting two and one-half days; no dysmenorrhea. After the age of 20 years, her menses were irregular with occasional long intervals of amenorrhea. At 41 years, her menses became regular at every twenty-eight days, but quite scant. At that time vasomotor symptoms developed, particularly frequent hot flushes.

Physical Examination.—Weight was 192 pounds; temperature, 98.3° F., pulse, 88; respiration, 28; blood pressure, 140/80. Patient was an obese, phlegmatic white female who did not appear acutely ill. The skin of the body was dry and warm with marked dermatographia. The palms of the hands were moist and warm. There was no tremor of the hands. The eyeballs exhibited a luster. The pupils were equal and regular and reacted promptly to light. There was no widening of palpebral fissure, exophthalmus or lid lag. The face was flushed; the tongue was slightly coated; the tonsils were large and swollen. The right lobe of the thyroid was about the size of a hen's egg, smooth in outline, and semisolid in consistency. The left lobe and isthmus were also enlarged but about one-third that of the right side. They had the same consistency as the right lobe. Chest examination revealed decreased resonance in right subscapular region and many crepitant rales in the middle lobe of the right side. Similar rales were audible in the corresponding area on the left side. There was no heart disease. The abdomen was negative. Neurologic examination showed no central nerve lesion.

Laboratory Findings.—Basal metabolic rate was plus 21 per cent. The x-ray of the chest showed no pulmonary tuberculosis but evidence of bronchiectasis. Patient was given Lugol's solution gtt. X three times daily for ten days and the basal metabolic rate was plus 11 per cent. A recheck one week later showed no further change in the basal metabolic rate. Despite the lowering of the basal metabolic rate from 21 to 11 per cent after taking iodine solution, we felt that the patient was not suffering from hyperthyroidism, but rather presented symptoms of menopause complicated by a bronchiectasis. We gave her estrogenic therapy consisting of 2,000 rat units of estrogen, twice a week. After twelve injections (six weeks), she stated that she felt much better and was free of vasomotor symptoms. Estrogenic therapy was continued. One month later her pulse rate was 68 per minute; the flushes were less frequent and less intense. For her pulmonary pathology she was referred to the chest clinic. When estrogen was omitted during the month of June, 1939, the vasomotor and nervous symptoms recurred within three weeks. Resumption of treatment with estrogen cleared her of these symptoms.

Comments.—We were dealing with a patient at the menopausal age who noticed an enlargement of the thyroid three years ago. The goiter apparently enlarged following a bronchopneumonia. A survey of the menstrual history showed that two years previously her menses were becoming scant and vasomotor symptoms became manifest. Despite the fact that her basal metabolic rate was plus 21 per cent, we felt that there was no emergency and a trial with estrogen would be indicated. Estrogen relieved her vasomotor symptoms which in the presence of an elevated basal metabolic rate were suggestive of thyrotoxicosis. This patient was thus spared the risk of an unnecessary thyroidectomy.

CASE 5.—Mrs. K. F., white, aged 47 years, was admitted to Temple University Hospital, Sept. 14, 1939, for thyroidectomy. Ten years ago she first learned that she had hypertension on being examined for life insurance; six years ago she had a blood Wassermann test which proved strongly positive, for which she received 7 intramuscular injections of bismuth salicylate. She failed to return for further treatment until the fall of 1939. Her blood Wassermann test was still strongly positive and her blood pressure was 240/136. Antisyphilitic treatment was started again; however, she continued to complain of nervousness, irritability, easy fatigability, and loss of weight, having lost 34 pounds in the past several months. She also suffered from pain over the precordium that radiated down the left arm. Patient has had an enlarged thyroid gland since the age of eleven years which in the past fifteen years grew larger; however, there has been no pain referable to the thyroid gland, no difficulty of swallowing or choking sensation. Menstruation com-

THE ADVANTAGES OF CONSERVATIVE OBSTETRICS AS SHOWN BY EXAMINATION SIX WEEKS POST PARTUM*

A REVIEW OF TWO THOUSAND CASES

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IN CARING for an obstetric patient, the accoucheur's greatest aim is to bring to a successful conclusion one of nature's processes, both from the point of view of the mother and of her baby. There is hardly a doubt in the minds of most of us that the end result of any obstetric case is a reflection of what has gone on not only after delivery, but in very great part what has been done prior to, and more particularly at the time of delivery. After delivery one can only aim to restore the pelvic organs to their physiologic normal condition in a reasonable period of time, usually considered by most obstetricians as six weeks.

The general attitude at the Boston Lying-in Hospital is one of conservatism, and it is because of this that during the past decade we have been able to place not only our morbidity, but the maternal and fetal mortality at the lowest level in the history of the hospital. Our morbidity averages 5.5 per cent.

The results we feel are due in some measure to the judicious use of analgesics in labor. It is apparent from our observation during the past ten years, that patients receiving medication are less likely to be unnecessarily interfered with, whereas in nonmedicated cases, the sympathy for the patient on the part of the doctor too often interferes with the management of normal labor. In other words, we give the natural forces of labor every opportunity to play a great part in the management of the obstetric case.

Manual dilatation in our opinion is an extremely serious procedure, both from the maternal and fetal standpoints. There were no patients in our series in whom the cervix was manually dilated; in fact, in the past five years in this hospital no cervix has been manually dilated. Williams,¹ Parker,² and Crist³ emphasize this principle in insisting on no manual dilatation of the cervix. To quote the latter: "There is no such thing as manual dilatation. Where such is attempted it results in manual separation or manual laceration." Blair⁴ very beautifully expresses his appreciation of the cervix when he says, "I cannot remember as an undergraduate that very much emphasis was placed on the cervix uteri. I think little attempt is made to give the undergraduate that attitude of respect, almost reverence, that is so necessary to treatment."

Too often inertia is considered an indication for manual dilatation. We prefer to treat this condition more conservatively. In some cases

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There was a fine tremor of the outstretched fingers of both hands. There was weakness of the quadriceps femoris muscle group. *Laboratory Findings:* Basal metabolic rate plus 35 per cent. After bed rest, sedatives, and iodine administration, patient had a subtotal thyroidectomy by Dr. W. Wayne Babcock. She had a stormy convalescence during which time the pulse rate increased to 160. However, she left the hospital considerably improved ten days after the operation. The histologic examination of the thyroid gland by Dr. Frank W. Konzelmann showed it to be a hyperplastic thyroid of the toxic type. Patient returned three months later after thyroidectomy. She gained weight, had less frequent attacks of palpitation and tired less readily; however, her nervousness and flushes continued. Pulse rate was 82. The blood pressure was 150/90. Menstruation became irregular, lasting only one day. She was placed on estrogen therapy, 2,000 rat units weekly and sedatives. After three months of this therapy, her nervousness decreased; the flushes ceased, and she was able to resume her household duties.

Comment.—This case represents a combination of manifestations of thyrotoxicosis and that of menopause. Although the operation cleared many of the symptoms, patient was not restored to complete health until her menopausal symptoms were attended to.

SUMMARY AND CONCLUSIONS

We have endeavored to correlate vasomotor symptoms of menopause with functional disturbances of the thyroid and pituitary glands. A patient at the menopausal age may suffer with hyperthyroidism alone, without having any true climacteric symptoms. More often, however, the vasomotor phenomena may mislead the clinician by simulating hyperthyroidism. The basal metabolic rate, particularly as a criterion for thyrotoxicosis, may lead one astray at the menopause. The result is often needless surgery. When such a patient is operated upon, the menopausal symptoms are not relieved, and the patient is exposed to the danger of developing postoperative myxedema. Thyroidectomy is rarely an emergency operation. Therefore, in borderline cases, before thyroidectomy is performed, the patient should be given the benefit of medical treatment, particularly estrogenic therapy. Stilbestrol may prove to be the simplest procedure.

These six cases are reported to illustrate the difficulties in diagnosis and management of borderline hyperthyroidism at the menopause. Three patients who had thyroidectomy failed to improve until estrogenic therapy was instituted. One of this group developed postoperative myxedema which complicated therapy. In three cases thyroidectomy was withheld and estrogenic therapy brought about complete amelioration of vasomotor symptoms.

We are indebted to the various members of the Medical and Surgical Staffs of Temple University Hospital for their cooperation.

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who have had a cesarean section are allowed up on the fourteenth day and are discharged on the seventeenth day. Patients are advised not to climb stairs for at least a week after discharge, and for a period of three weeks after discharge they are encouraged to have bidaily rest periods. The improvement in patients with subinvolution receiving hot vaginal douches, coupled with the findings at six weeks' post partum of many patients with moderate degrees of subinvolution, and eroded and edematous cervixes, led us to the policy of instructing all patients to start douches on leaving the hospital, continuing them until their six weeks' return visit. If, on discharge examination, a patient is found to have a retroversion, she is further instructed to take knee-chest exercises. These instructions are distributed to each patient on a type-written sheet, so there may be no doubt in the mind of the patient as to what she is to do.

To note our end results statistically we studied the records of 2,000 consecutive admissions. Parity and age distribution are shown in Tables II and III.

TABLE II. PARITY DISTRIBUTION

	i	ii	iii	iv	v	vi	vii	viii	ix	x+
Cases	1224	383	152	104	53	36	25	9	7	7
Per cent	61.2	19.15	7.6	5.2	2.65	1.8	1.25	0.45	0.35	0.35

TABLE III. AGE DISTRIBUTION

	UNDER 20	20-24	25-29	30-34	35-39	40+
Cases	160	731	582	320	163	44
Per cent	8	36.55	29.1	16	8.15	2.2

Much variation in the treatment of the perineum is discussed in the literature.

Potter⁷ advises against episiotomy but prefers to iron out the perineum with green soap, believing that this prevents shock, and that the elasticity of the muscle is not destroyed. Danforth,⁸ Greenhill,⁶ Kelley,⁹ Sellers and Sanders¹⁰ advise routine episiotomy. Cooke¹¹ favors median episiotomy, but states neither is necessary in 10 per cent of primiparas. Lubin¹² prefers episiotomy to laceration but states that 50 per cent of all deliveries have an intact perineum. We believe this statement may be true but the levators beneath the mucous membrane are undoubtedly separated in a large percentage of these cases, resulting in a relaxed pelvic floor. Routine episiotomy will protect the patient in later years from the necessity of perineal repair. The incision of the perineum in the median raphe seems to be ideal. Michaelis first described this in 1799. In our series, 40.8 per cent had median against 17.7 per cent of mediolateral episiotomies. The remaining 41.5 per cent are comprised of lacerations and intact perineae. To us this latter percentage seems high as compared to that in private practice. This percentage of lacerations and intact perineae is due to two causes: first, a good number of these patients are delivered by externs at home where routine episiotomy is not practiced for obvious reasons; and second, many of these patients were previously not treated with an episiotomy and started out with a relaxed perineum. The median episiotomy has the advantage over all others in that it heals more readily, causes much less discomfort, and anatomically is a mere separation of the levators rather than a severing of their fibers. Cooke¹¹ agrees with the above principle, because he also believes severed transverse muscle bundles do not heal as readily as simple separation of the levators. At this hospital we advocate routine median episiotomies unless contraindicated.

where the cervix is not taken up, sedation is best; in others fairly well advanced in labor, it is best treated by stimulation. If the cervix is partially dilated and effaced, simple rupture of the membranes often advances labor satisfactorily; small amounts of pituitary extract, namely in one minim doses, when not contraindicated, are a valuable adjunct, certainly far more so than attempted manual dilatation.

It is our policy to deliver as many patients as possible normally or by low forceps. High forceps have been abolished. Internal podalic version has only a rare indication. Midforceps are but seldom necessary. Breech extractions are fast disappearing because of the policy of practicing external version after seven months. We allow two hours in the second stage without progress, at which time an episiotomy, preferably a median one, is made, and when possible the baby is delivered normally with the aid of superfundic pressure. If this fails, low forceps are applied. Other than maternal and fetal distress there are only two usual indications for forceps extraction at full dilatation, namely, prematurity and patients with organic heart disease. DeLee⁵ advocates for the specialist what he terms prophylactic forceps. On the other hand, Greenhill⁶ advocates at least one hour in the second stage without progress. As noticed in Table I, 64 per cent of our series were delivered normally and 25.85 per cent by low forceps. Four per cent of the remaining were delivered by cesarean section. The use of the latter in cases of suspected cephalopelvic disproportion has been governed by successive lateral Thom's x-rays. We feel that this conservatism contributes considerably to more satisfactory end results.

TABLE I. METHOD OF DELIVERY

	NORMAL DELIVERY	PRIMP. LOW FORCEPS	MULTIP. LOW FORCEPS	ABORTION	BREECH	MULTIPLE PREGNANCY	CESAREAN SECTION	VERSION	BRAXTON HICKS VERSION	MID-FORCEPS
Cases	1280	471	46	22	41	24	80	8	11	17
Per cent	64	23.55	2.3	1.1	2.05	1.2	4	0.4	0.55	0.85

As will be noted later (Table VI), 86.5 per cent had a satisfactory end result at six weeks. We attribute this to a lack of manual interference during labor plus routine post-partum care which our patients have received for some time. This routine begins with having our patients in a semisitting position soon after delivery, encouraging the patient to move from side to side frequently, and the beginning of exercises on the third day post-partum, all of which, we feel, aid involution. Ergot is not given routinely, but in patients who show evidence of subinvolution one drachm of fluid extract of ergot is given t.i.d. for three days. Patients still showing evidence of subinvolution on the tenth day are then started on two-gallon sterile douches at 110° F. Marked improvement is usually immediately noticed. Normal patients are allowed up on the tenth day and discharged on the fourteenth day. Patients

a temperature of 100.4° F. or over on two consecutive days, regardless of cause or time in the puerperium. Our end results, we believe, are good evidence in favor of the pursuance of these conservative policies. As noted in Table VI, 68.3 per cent of our patients at six weeks had a completely healed cervix, 18.2 per cent had a very slight circumoral erosion with no eversion or laceration. Most of these latter would ordinarily be considered within normal limits. Thus 86.5 per cent of our patients at six weeks postpartum had a satisfactorily healed cervix. As a corollary to this, Table VII shows that at six weeks 90.75 per cent of our patients had either no leucorrhea or insufficient to necessitate the use of a perineal pad.

TABLE VI. CONDITION OF CERVIX AT SIX WEEKS' EXAMINATION

	HEALED AND NO EROSION	CIRCUMORAL EROSION	EROSION ANTERIOR LIP WITH EVERSION	MODERATE EROSION BOTH LIPS WITH EVERSION	DEEP BILATERAL LACERATION	UNILATERAL LACERATION	STELLATE	ENDOCERVICITIS	BOGGY
Cases	1366	364	52	163	14	3	20	23	4
Per cent	68.3	18.2	2.6	8.15	0.7	0.15	1	1.15	0.2

TABLE VII. PRESENCE OF LEUCORRHEA SIX WEEKS POST PARTUM

	NONE	SLIGHT BUT NO PAD	MODERATE NO PAD	MODERATE WITH PAD	PROFUSE
Cases	1235	580	58	124	3
Per cent	61.75	29	2.9	6.2	0.15

As far as is possible, a fairly definite routine is followed in the treatment of the cervix at six weeks. If there is a small circumoral erosion, the vagina and the cervix are wiped clean, and 25 per cent silver nitrate is applied to the erosion. The patient is instructed to begin daily douches one week following this treatment and to continue them daily for five weeks when she returns for another check-up. If the erosion has improved, silver nitrate may be applied again. However, if there has been no improvement then the erosion is treated with electrocautery. Instructions following this are the same as that following silver nitrate. The end results of this treatment are shown in Table VIII where it is

TABLE VIII. TREATMENT OF CERVIX AT EXAMINATION SIX WEEKS POST PARTUM

	NONE	SILVER NITRATE	CAUTERY	SILVER NITRATE PLUS CAUTERY	SILVER NITRATE TWO TIMES PLUS	CAUTERY TWICE	CAUTERY THREE TIMES PLUS
Cases	1381	303	126	101	30	36	2
Per cent	69.05	15.15	6.3	5.05	1.5	1.8	0.1

noted that 69.05 per cent of our patients required no treatment at six weeks' examination; 15.15 per cent had such a slight erosion that one

TABLE IV. TREATMENT OF PERINEUM AT DELIVERY

	LACERATION FIRST DEGREE	LACERATION SECOND DEGREE	LACERATION THIRD DEGREE	MEDIAN EPISIOTOMY	MEDIO- LATERAL EPISIOTOMY	INTACT
Cases	44	43	5	816	354	741
Per cent	2.2	2.15	0.25	40.8	17.7	37.05

It will be noted in Table V that there is a very low percentage of poor results in perineal support. The preparation prior to delivery, we believe, has not too little influence on this fact. The routine use of enemas at the onset of labor, thoroughly emptying the lower bowel, abolishes certain risk of infection by eliminating the expression of feces over the perineum as the head descends in the pelvis. Furthermore, the use of the lithotomy position for delivery with the lower end of the table dropped aids toward keeping a sterile field, as well as allowing for an excellent exposure.

TABLE V. CONDITION OF PERINEUM AT SIX WEEKS' EXAMINATION

	HEALED AND GOOD SUPPORT	HEALED AND MODERATE SUPPORT	MODERATELY RELAXED	MARKEDLY RELAXED WITH CYSTO- CELE AND RECTOCELE	PERINEAL FISTULAS	RECTO- VAGINAL FISTULAS
Cases	1694	108	144	46	8	2
Per cent	84.7	5.4	7.2	2.3	0.4	0.1

Intermediate repairs of old relaxed perineae are advocated by Tracy,¹³ Crist,³ Gayden and Plass,¹⁴ Hanna,¹⁵ Pride,¹⁶ and Kelley.⁹ It has not been the policy of the Boston Lying-in Hospital to routinely follow such procedure, because there are new interns entering the service each month. It is the private opinion of the authors that in cases of relaxation of the perineum a reasonably satisfactory result may be obtained by such a procedure. The result, however, is not considered as being as satisfactory as if the patient had had repeated episiotomies or gynecoplastic repair after the childbearing age.

Conservatism is also the rule in treatment of the cervix. We do not inspect cervixes at the time of delivery, nor do we advocate immediate suturing of the cervix except when there is hemorrhage. We definitely feel that the cervix should be inspected only in certain cases, even in the absence of hemorrhage, namely, patients with old cervical repairs, previous cesarean section, breech extraction, internal podalic version, and in cases where there has been manual dilatation. As previously stated, the latter three occur with great infrequency in our hospital. In our 2,000 cases, it was found necessary to suture the cervix in 23 cases, only one and one-tenth of one per cent. It may be stated here that of these 23 cases, only one received pituitrin before the cervix was fully dilated, and in this case, only one minim was given for inertia when the cervix was four-fingers dilated. Further, in these 23 patients, 7 were febrile, a morbidity of 30 per cent, practically six times higher than the morbidity of the entire group, which averaged 5.5 per cent. This morbidity is not a corrected one and is based on any patient with

In primiparas with lacerated cervices not repaired, he reports a morbidity of 8.1 per cent as contrasted with 16.1 per cent in the repaired cases; the occurrence of post-partum cervical infections is 6 per cent in primiparas where the lacerated cervix was not repaired, as against 5.4 per cent in primiparas where the cervix was repaired, certainly not an appreciable difference. With these figures, Goff concludes that: "Immediate trachelorrhaphy though the immediate and remote results are not ideal is a valuable prophylactic procedure against post-partum cervical infections and their sequelae." Hanna,¹⁵ admitting that the birth canal is very susceptible to infection and therefore should be treated as a surgical wound, advocates immediate repair of the cervix even in home deliveries. Speidel²⁶ goes so far as to use forty-day No. 2 chromic catgut. On the other hand, we find that others, such as Cooke,¹¹ Adair,²⁷ Hofbauer,²⁸ and Crist,³ advocate suture of the cervix only in the presence of hemorrhage. Some authors prefer the intermediate type of repair. Tracy¹³ and Williams¹ advise repair five to ten days post partum. Dickinson, as reported by Danforth,²⁹ repairs at two to three days post partum, and Hirsh and Coffee, as reported by McCarley,²⁴ repair five and ten days post partum, respectively. We feel that in the light of our present results this is an unnecessary added risk to the patient, for it certainly necessitates a second anesthesia and operation.

Our immediate post-partum treatment has been already outlined in detail above. As was stated previously in this paper, all patients at the time of the thirteen-day examination are advised to take douches daily, regardless of the presence or absence of retroversion. The literature is conspicuous by the absence of discussion in the use of douches post partum. Prior to the routine use of douches we noted that a large percentage of patients at six weeks showed subinvolution and large, boggy, and eroded cervices sufficient to require depletion before cautery could be safely used. This led us to believe that if depletion by douching were started early in the puerperium, any necessary treatment would not be delayed at the six weeks' examination. We were pleased to find in our series a very small percentage of subinvolved uteri, namely 2.9 per cent. At the six weeks' examination, patients with retrodisplacement were treated in one of several ways. First, those with asymptomatic retroversions were not given any treatment but were told to return should symptoms, such as backache, menorrhagia, or dysmenorrhea, occur. Second, those with a retroversion having any of the above symptoms associated with an enlarged uterus were treated with a Smith Hodge pessary after the uterus had been replaced manually or with the aid of a tenaculum on the cervix. These patients as far as could be controlled wore the pessary for three months, changing it at six-week intervals. The patient was instructed to take daily douches throughout this period and was told to return four to six weeks after the three-month period of wearing the pessary for a final check-up. Many of these patients did not return presumably because of the absence of symptoms. At this subsequent examination, patients who were found to have an anterior uterus were considered as permanently cured, while those who had asymptomatic third-degree retroversions were considered as probably temporarily cured and were instructed to return should symptoms recur. Only patients showing a retroversion with symptoms having been relieved with the pessary were referred for suspension.

Knee-chest exercise is a recognized and practiced method of correcting third-degree retroversions. Unfortunately we are unable to report a

treatment with 25 per cent silver nitrate was sufficient to heal the cervix and enable them to be discharged at the next visit. After electrocautery, 6.3 per cent needed no further treatment. In other words, 90.5 per cent of our patients showed a healed cervix at twelve weeks post partum. Further, 5.05 per cent received cautery once following application of silver nitrate. The reason in most cases for this procedure is the policy of never using cautery immediately preceding an impending catamenia. These patients were instructed to return for cautery at the cessation of their menstrual flow.

TABLE IX. RETURN VISITS

	DIS- CHARGED AT SIX WEEKS	1 VISIT AND DIS- CHARGED	2 VISITS AND DIS- CHARGED	3 VISITS AND DIS- CHARGED	4 VISITS AND DIS- CHARGED	5 VISITS AND DIS- CHARGED	6 VISITS AND DIS- CHARGED	DID NOT RETURN
Cases	1382	373	146	53	21	3	4	160
Per cent	69.1	18.6	7.3	2.65	1.05	0.15	0.2	8

This foregoing routine has further proved more gratifying as evidenced by the fact that 69.1 per cent were discharged at six weeks without any treatment and 18.6 per cent after one subsequent visit, or a total of 87.7 per cent were discharged within a period of twelve weeks post partum.

We, therefore, feel that 25 per cent silver nitrate and the electrocautery are important as valuable adjuncts in the treatment of the postpartum cervix.

Along with cautery, conization of the cervical canal, as described by Hyams^{17, 18} for the treatment of chronic cervicitis, is very valuable. General anesthesia is not needed for this procedure. Fifty per cent cocaine in the canal for five minutes is sufficient to give adequate local anesthesia.

The foregoing policies and the resultant figures are not at variance with other authors as noted in a review of the literature of the past ten years.

Goff¹⁹ reviewed the subject historically, noting that it was Sir James Simpson in 1851 who pointed out that cervical lacerations were a frequent occurrence and occasionally unavoidable. This was further described by Robert Ellis of London in 1861. However, it was not until 1874 that Montrose A. Pallen performed immediate suture of the cervix at two weeks. The indications here were also hemorrhage. Then in 1884 Carl Schroeder described his operation. A number of men, Bernstein,²⁰ Danforth,⁸ Emrick,²¹ Galloway,²² Goff,¹⁹ Hanna,¹⁵ Kelley,⁹ MacFarlane,²³ McCauley,²⁴ Miller,²⁵ Potter,⁷ Pride,¹⁶ Sellers and Sanders,¹⁰ and Speidel²⁶ believe in the immediate repair of the cervix. Potter⁷ goes one step further in stating that the cervix after manual dilatation has a much better appearance than that of a cervix not manually dilated. This, of course, is contrary to our opinion. Danforth⁸ sutures any laceration of 2 cm. whether or not bleeding is present. He reports 75 per cent of good results. However, C. B. Reed⁸ in discussing Danforth's work felt that in many of his cases the cervix was too edematous for immediate suture, and in these cases the sutures cut through. Reed further states that in some cases he has repaired one side and not the other due to edema, and later found the unsutured side healed. Goff¹⁹ reports many figures, some of which seem contrary to his conclusions. His morbidity in repaired cervices is at least twice as great as in his unrepaired cases.

were permanently cured, which compares favorably with figures reported by Cooke³² and Abbott.³³ 26.8 per cent of these patients had a retroversion after treatment but were asymptomatic. These we considered as relieved though retroversion still persisted. We may, therefore, conclude that 90.2 per cent of the patients with third-degree retroversions treated by pessary were either relieved of their symptoms or permanently cured. There were three patients of this group whose uteri remained retroverted in spite of treatment and were referred for suspension. Two of the total number had an anterior uterus after treatment but continued to have symptoms. These we felt were definitely associated with relaxation of the pelvic girdle. With a high percentage of successful results as noted above, we would like to emphasize the importance of the Smith Hodge pessary not only as a method of treatment but as a diagnostic procedure prior to suspension.

Harris, and associates,³⁴ in an experimental study of 8 cadavers, found that the upper two-thirds of the paravaginal tissue or the lower two-thirds of parametrial tissue were necessary for uterine support. Section of the round, ovarian, and infundibulopelvic ligaments, plus the upper third of the broad ligaments, had no effect on uterine descent as long as the above-mentioned structures were intact. With this fact in mind it seems logical to believe that depletion douches may strengthen the paravaginal and parametrial tissues.

Parker² emphasizes the importance of rest, exercise, little or no step walking, knee-chest position, kangaroo walk, as valuable in aiding a return to normal. He states that normal involution is not complete for twelve weeks and further, that from 18 to 42 per cent of women have retroversion, half of which are symptomless. Cook³² believes that the knee-chest position and similar exercises, such as the elephant walk, have greatly reduced the number of patients needing a pessary. He believes that 60 to 70 per cent of puerperal retroversions have a permanent cure when the pessary is used at six weeks' post partum. Galloway²² advocates back rest and face position on third day, wheel chair on sixth, steps on ninth, and discharge on the twelfth. His patients do calisthenics after lochia has disappeared and knee-chest exercises twice a day for ten minutes until six to eight weeks' return. Kanter and Klamman³⁵ advise, as a preventive for retroversion to give ergot for three days, turn patient from side to side, have her lie on the abdomen, and to sit up on the fifth day on a back rest. Contrary to the above belief is the experience of Schauffler³⁶ who reports two small series, one of 84 untreated patients in whom 34.5 per cent had resultant retroversion and the other 72 treated patients, with 47.2 per cent of resultant retroversion. The treated patients followed a routine of ventral position in bed, knee-chest on eighth day twenty minutes twice a day, the camel walk on the eighteenth day, and abdominal exercises in the upright position. It has been estimated by various observers that the incidence of retroversion is between 18 and 40-odd per cent. Peckham³⁷ reports 18.25 per cent retroflexed at six weeks' postpartum and 16.82 per cent at one year. Eichner³¹ reports 25.1 per cent at the first examination, three weeks' post partum, the percentage increasing with parity from 20 to 41.2 per cent. In quoting Stacey, Abbott³³ states that there are 20 per cent of retroversions in nonparous, and from 30 to 35 per cent in parous women. He also states that 50 per cent of the patients have no symptoms. Backache, per se, in the presence of retroversions, has been generally over-emphasized and believed to be directly associated with the displacement. This belief has led to too many unwarranted surgical procedures by the general surgeon. We feel it bears repeating that too little emphasis is placed on the use of the Smith Hodge pessary, not only as a curative, but more especially as a diagnostic procedure. Abbott³³ reports 50 patients operated upon for backache, with 16 still having pain after the suspension, and states that this indicates the necessity of an orthopedic study, and further recommends the pessary as a test to see what may be expected after an operation. Peterson³⁸ also emphasizes the value of the orthopedic relation

sufficient group who had conscientiously taken knee-chest exercises. However, it is our opinion that knee-chest exercises in themselves do not cure more than a small percentage of third-degree retroversions.

Moses,³⁰ in a critical study at the Florence Crittenden Home, reports on a controlled series of 210 patients who received no treatment and 210 patients who received knee-chest exercises from the tenth day post partum. At the end of six weeks' post partum, his findings were exactly the same in both groups, namely 64.7 per cent were anterior and 35.2 per cent were posterior.

In evaluating our end results, one notes from Table X that 11.45 per cent of our patients had a third-degree retroversion, and of this group three-fourths, as shown in Table XI, were asymptomatic.

TABLE X. UTERUS AT SIX WEEKS POST PARTUM

	ANTERIOR FREELY MOVABLE, NORMAL SIZE	FIRST DEGREE RETROVERSION, NORMAL SIZE	SECOND DEGREE RETROVERSION, NORMAL SIZE	THIRD DEGREE RETROVERSION, ENLARGED	ANTERIOR AND ENLARGED	PROLAPSED UTERI	TOTAL THIRD- DEGREE RETROVERSION
Cases	1246	178	280	11	47	20	229
Per cent	62.3	8.9	14	.55	2.35	1	11.45

TABLE XI. CLASSIFICATION OF RETROVERSIONS

	TOTAL THIRD-DEGREE RETROVERSIONS	ASYMPTOMATIC	SYMPTOMATIC
Cases	229	177	52
Per cent		77.28	22.72

TABLE XII. TREATMENT OF SYMPTOMATIC THIRD-DEGREE RETROVERSIONS WITH RESULTS

	PESSARY FOR THREE MONTHS	ANTERIOR AFTER TREATMENT WITHOUT SYMPTOMS	ANTERIOR AFTER TREATMENT WITH SYMPTOMS	POSTERIOR AFTER TREATMENT WITHOUT SYMPTOMS	POSTERIOR AFTER TREATMENT WITH SYMPTOMS
Cases	35	20	2	11	2
Per cent		57.1	5.7	31.5	5.7

TABLE XII-A. TREATMENT OF RETROVERSIONS CONTINUED

	PESSARY WORN LESS THAN THREE MONTHS	ANTERIOR AFTER TREATMENT WITHOUT SYMPTOMS	POSTERIOR AFTER TREAT- MENT WITHOUT SYMPTOMS	POSTERIOR AFTER TREAT- MENT WITH SYMPTOMS
Cases	17	13	3	1
Per cent		76.4	17.4	5.8

The treatment of the remaining 22.72 per cent of symptomatic cases is shown in Table XII and XII-A; 63.4 per cent of these patients with third-degree retroversions, wearing a pessary for three months or less,

It is interesting to note that of the 2,000 patients studied only 6.25 per cent were referred to the hospital for some type of operation. The reasons for transferring to the hospital are shown in Table XIV.

TABLE XIV. PATIENTS REFERRED FOR OPERATION

	REPAIR OF CERVIX	VAGINAL PLASTIC	FIBROIDS	OVARIAN CYSTS	SUSPENSION	STERILIZATION	OTHER PATHOLOGY	NONE
Cases	45	13	3	1	3	3	58	1875
Per cent	2.25	0.65	0.15	0.05	0.15	0.15	4.9	93.75

CONCLUSIONS

1. Two thousand consecutive admissions to the Boston Lying-in Hospital have been studied.
2. Emphasis is placed on conservatism in obstetrics as being most instrumental in the future well being of the patient.
3. A morbidity of 5.5 per cent is reported.
4. Analgesics in labor are recommended.
5. Manual dilatation of the cervix is discouraged.
6. The incidence of operative obstetrics has been kept very low.
7. Episiotomy, preferably median, is encouraged as a routine procedure.
8. Immediate repair of the cervix except in cases of hemorrhage is considered as unnecessary and creating an unnecessarily high morbidity.
9. Use of vaginal douches, silver nitrate, and electrocautery is encouraged.
10. Third-degree retroversions should be treated only when symptomatic and then by the use of the Smith Hodge pessary before resorting to surgery.
11. The bladder should be watched carefully during labor and immediately afterwards and treated to prevent atonicity.

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to backache even in the face of retroversion and reports a decrease in operative incidence on retroversion due to this fact. Fullerton³⁹ states that backache is more often due to a strained pelvic girdle than to a retroversion, and recommends a strong abdominal girdle, giving support at the level of the greater trochanters. In a paper by Sturmdorf,⁴⁰ Ward is quoted as saying that backache in 15 per cent of gynecologic patients is of orthopedic or of nonsurgical nature. In the same paper Theilhaber of Munich, and Cabot of Boston emphasize the existence of symptomless uncomplicated retroversion of the uterus. Bullitt⁴⁰ estimates that 15 per cent of the surgically corrected retroversions continue to suffer from backache. Hurd⁴⁰ in 1,000 patients with retroversion found only 17 per cent who complained of backache and concluded that this fails to verify backache as a classical symptom of retroversion. Sturmdorf in further quoting Hurd reports that out of 100 patients operated upon there were 40 per cent immediate failures and 12 per cent symptomatic failures.

A fair-sized group of our patients were found to have symptoms directly referable to pelvic joints attendant upon pregnancy. These patients were treated orthopedically. Discussion of treatment of patients with symptomatic relaxation of the pelvic joints is, of course, beyond the realm of this paper. However, we would like to emphasize the importance of this condition and the possibility of confusing the symptoms of separation of the symphysis and of third-degree retroversion.⁴¹

It has not been until recent years that much attention has been placed on the care of the bladder during and after labor. It was not uncommon ten years ago to find a considerable number of post-partum atonic bladders, necessitating much in the way of treatment. Though we know that a full bladder militates frequently against normal progress of labor, we find it essential not only from this point of view, but also from the possible resultant atonic bladder, to catheterize, periodically, the patient during labor, especially when analgesic drugs have abolished the normal stimulus to void. Needless to say, all patients are catheterized just before delivery. Following delivery the patient is catheterized at eight hours if unable to void. Subsequent to this, if at the next eight-hour period the patient voids only a small amount, she is catheterized for residual, and if she has a residual of over 2 to 5 ounces, her bladder residual is checked carefully after each voiding until the residual is under two ounces. If, however, at the end of seventy-two hours, there is still a residual of over 5 ounces an inlying catheter is inserted, being kept in position for five days after which it is removed and the patient is checked eight hours later for residual. It is comparatively rare to note a residual after this treatment. In fact, the use of the inlying catheter has been very infrequent during the past half dozen years. This routine as described above has greatly reduced the incidence of atonic bladders with resultant infection. In Table XIII one notes that 95.25 per cent of our patients at six weeks had no bladder symptoms or dysfunction.

TABLE XIII. URINARY SYMPTOMS

	NORMAL	DYSURIA	FREQUENCY	FREQUENCY AND DYSURIA	INCON- TINENCE	URGENCY
Cases	1905	58	12	3	18	6
Per cent	95.25	2.9	0.6	0.3	0.9	0.3

of consolidation. The only recorded blood examination was a white count of 22,500. A moderate to marked pallor of the conjunctivae was noted, and later the sclerae had an icteric tinge. There was an old scar over the left tibia, 3 by 5 cm. The sputum contained relatively few pneumococci and could not be typed with any known sera. The urine, Wassermann, and blood cultures were negative.

The temperature remained around 102° F., and the respiration varied between 40 and 20 per minute. Since typing with known pneumococcic sera failed, the patient was given sulfapyridine therapy on the next day. On Jan. 19, 1939, at 10:30 A.M. the membranes ruptured spontaneously and the patient went into labor. The fetal heart tones disappeared about an hour after onset of labor. After sixteen hours she delivered a somewhat macerated stillbirth spontaneously. The post-partum blood pressure was 140/92. Her immediate condition was only fair; she failed rapidly and died six hours later, fifty-six hours after admission.

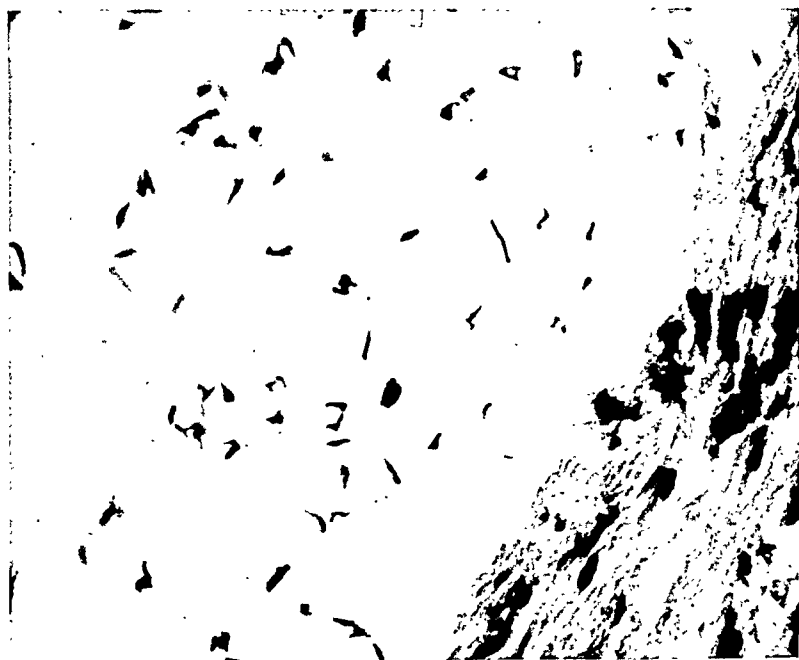


Fig. 1.—Sickle-shaped red cells seen in the intramuscular spaces of the myometrium. The latter shows hypertrophy changes of pregnancy.

Post-Mortem Examination.—(Prosector: J. D. Kirschbaum.) The important features of the anatomic diagnosis were as follows: sickle-cell anemia, marked hepatosplenomegaly, post-partum beginning involution of the uterus, parenchymatous degeneration of the myocardium, atelectasis of the lungs, slight passive congestion of the left lower pulmonary lobe, marked passive congestion of the liver, spleen, and kidneys, and hyperplastic bone marrow.

The microscopic sections of the spleen revealed very compact lymphatic tissue without signs of proliferation and forming small concentric, sharply demarcated coats around the trabeculae and arterioles. Most of the sinusoids of both the liver and spleen were stuffed with conglomerated red blood cells of sickle shape. There was very little phagocytosis of the red blood cells. The bone marrow showed very active myelopoiesis and erythropoiesis with numerous megakaryocytes. All the tissues in the body showed sickling of many erythrocytes. Sickle-shaped red cells were seen within the muscle spaces of the post-partum uterus (Fig. 1).

CASE 2.—M. W., a 30-year-old, colored, gravida i, had her last menstrual period Dec. 23, 1938, and was due on Sept. 30, 1939. Her prenatal course had been practically normal. She had attacks of so-called “rheumatic fever” ever since the

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SICKLE-CELL ANEMIA IN PREGNANCY*

A REVIEW OF THE LITERATURE AND REPORT OF SIX CASES

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SICKLE-cell anemia is an hereditary blood dyscrasia peculiar to the negro race, although there have been reports of isolated cases in white families (Greenwald and Burrett¹). The first complete description of this disease was given by Herrick² in 1910. Although the blood of 8 per cent of the negroes has a sickle-cell trait, only 0.8 to 1 per cent develop true sickle-cell anemia. The occurrence of this type of anemia in pregnancy has been reported only on a few occasions.

Sydenstricker³ found sickled red cells in the cord blood of two infants whose mothers had this disease. Yater and Mollari,⁴ Lash,⁵ Richter,⁶ Sharp and Schleicher,⁷ Killingsworth and Wallace,⁸ Lewis,⁹ Sodeman and Burch,¹⁰ and Page and Silton¹¹ all contributed case reports of this anemia during pregnancy. Our 6 cases, included herewith, make a total of 17 reported pregnancies with this anemia. A study of these 17 cases with a consideration of their previous pregnancies makes it possible for the first time to offer a detailed analysis of how this anemia affects pregnancy.

CASE REPORTS

CASE 1.—E. W., a 22-year-old, colored, gravida i, was admitted to the Obstetric Service of the Cook County Hospital on Jan. 17, 1939. She complained of chilly sensations for six days, followed by a mild cough with white mucoid expectoration and chest pain in the lower right anterior surface. Last menstrual period occurred April 4, 1938, and she was now full term. Past history was essentially negative except for attacks of joint pains during childhood that resembled rheumatic fever.

The patient appeared acutely ill and markedly dyspneic. Her temperature was 101.6° F., pulse 108, respirations 60, and blood pressure 128/84. The lungs showed a faint friction rub in the right base anteriorly with impaired resonance and diminished breath sounds over the right lower lobe posteriorly. The fundus was three fingers below xiphoid, position L.O.A., and fetal heart tones were 160. A tentative diagnosis of right lower lobe pneumonia was made. Roentgenogram of the chest showed only moderate increase of the markings bilaterally with no significant areas

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revealed: polymorphonuclears 61 per cent, metamyelocytes 1 per cent, basophiles 1 per cent, lymphocytes 28 per cent, and monocytes 9 per cent. Eight per cent of the red blood cells were nucleated. Anisocytosis was three-plus, macrocytosis two-plus, and polychromatophilia one-plus. The reticulocyte count was 26.8. A diagnosis of left lower lobar pneumonia in a patient six and one-half to seven months pregnant with sickle-cell anemia was made. She was treated with sulfapyridine, fluids, and two blood transfusions, and she made a quick uneventful recovery within two weeks. She was discharged back to the prenatal clinic where her prenatal course was observed.

On Jan. 3, 1940, she was readmitted to the hospital because of a sudden rise in blood pressure to 170/128, dizzy spells for three or four days, and pedal edema for the past week. The urine showed three-plus albumin and a few red blood cells. The hemoglobin was now 50 per cent, red blood count 2,460,000, white blood count 14,750, with 66 per cent sickling and 21 per cent nucleated red blood cells. The differential count was normal. Blood chemistry showed the nonprotein nitrogen to be 28 mg. per cent, and the uric acid slightly elevated to 6.8 mg. per cent.

She was placed on conservative toxemia management. Fundoscopic examination showed changes in the eyes that were interpreted to be due to arteriosclerosis with a possible syphilitic background. Her blood pressure gradually improved; after nine days it was 120/78 and she was discharged back to the prenatal clinic. The diagnosis at that time was a pre-eclamptic toxemia.

Five days later she was admitted to the hospital for the third time with ruptured bag of waters and in active labor. Her blood pressure was now 186/122. She was treated with intravenous hypertonic dextrose and magnesium sulfate and morphine. She delivered spontaneously a three-pound twelve-ounce female infant after a labor of five hours and ten minutes. The baby was in good condition, and blood counts made on the infant at various intervals were normal. The patient's post-partum course was complicated only by the development of a low grade endometritis which gradually subsided. Her blood pressure dropped to 142/90 on the fourth day. She received two blood transfusions, 500 c.c. each, during puerperium and was discharged on the eleventh day.

The blood count on the day of discharge revealed 45 per cent hemoglobin, 2,090,000 red cells, and 13,600 white cells. The stained smear showed 75 per cent polymorphonuclears, 1 per cent basophiles, 17 per cent lymphocytes, 6 per cent monocytes, 1 metamyelocyte, 3 nucleated reds, presence of target cells, hypochromia one-plus, polychromatophilia two-plus, anisocytosis with macrocytosis and poikilocytosis two-plus. The urine showed no albumin on discharge.

CASE 4.—A. O., an 18-year-old, colored, gravida i, menstruated last on Feb. 1, 1940. One week before admission to the hospital, she felt feverish, developed marked urinary frequency, and had a backache on the right side. She was admitted to the hospital on June 27, 1940, with a temperature of 102.6° F., and pulse 120. Her chief complaint at this time was backache. The uterus was about the size of a six months' gestation. The patient appeared frail and delicate; otherwise the physical findings were negative.

The admission diagnosis of pyelitis was confirmed by a catheterized urine specimen that showed many clumped pus cells. Urinary culture revealed *B. coli*. The initial blood examination showed a red count of 2,900,000, hemoglobin 51 per cent (Sahli), and a white count of 20,100. One week later the red count was 2,220,000, hemoglobin 42 per cent (photoelectric colorimeter), and the white count 47,000. The differential count enumerated 91 per cent polynuclears, of which 39 had band forms, 3 per cent metamyelocytes, and 6 per cent lymphocytes. In addition, anisocytosis, polychromatophilia, marked basophilic granulations of the granulocytes or a toxicity of four-plus, and marked sickling was observed.

During her stay in the hospital, the essential therapy was directed to overcome the infection and the anemia. Sulfanilamide was given for the infection. For the anemia, she was given six transfusions of 500 c.c. each of citrated blood, liver extract, iron ammonium citrate, nicotinic acid, dilute hydrochloric acid, and high caloric diet when the patient was able to retain foods.

age of four, with frequent recurrences of joint pains. Her sclerae were frequently icteric. This was more pronounced whenever she had a "cold." None of her five brothers and sisters lived to be over thirty-one years of age. On Aug. 31, 1939, she was admitted to the hospital with the complaints of chills for four days, followed by a dry hacking cough, pain in the chest, and shortness of breath.

She was acutely ill with temperature of 102.6° F., pulse 136, respirations 36, and blood pressure 124/106. The sclerae were icteric and the conjunctivae pale; her teeth were in poor condition and pharynx was slightly reddened. The respirations were shallow and limited on the left side, with increased tactile and vocal fremitus, tubular breathing, dullness, pectoriloquy over the left lower lobe. The spleen was palpable. The uterus was three fingers below the xiphoid; fetal position was L.O.T. and fetal heart tones were 150 per minute.

The laboratory findings on admission were as follows: The urine contained albumin three-plus, urobilinogen four-plus, and scattered white blood cells and hyaline and granular casts. The blood serum was highly colored and the icteric index showed thirty units. Hemoglobin was 50 per cent (Sahli), red cell count 2,100,000, and white cell count 37,000. Differential white count showed 87 per cent polymorphonuclears, 8 per cent lymphocytes, and 5 per cent monocytes. There was also 8 per cent sickling and 23 per cent immature red blood cell forms in the dry smear. A chest x-ray taken that day revealed some cardiac enlargement and findings somewhat suggestive of bronchopneumonia. A marked osteoporosis in the bones of each shoulder joint was noted.

The clinical diagnosis of sickle-cell anemia in the acute phase, left lower lobar pneumonia, and moderate toxemia of pregnancy was made. The patient improved gradually with sulfapyridine therapy supplemented by oxygen and repeated blood transfusions. Typing for pneumococci was unsuccessful. Two days after admission the fetal heart tones could no longer be heard. The following day the patient went into labor and six hours later spontaneously delivered a macerated stillbirth that weighed slightly over five pounds. The post-partum blood pressure was 110/74. The improvement continued after repeated transfusions which totaled 4,000 c.c. of preserved citrated blood.

About three weeks post partum, the blood study revealed: hemoglobin 68 per cent, red cell count 3,660,000, white cell count 10,500, and reticulocytes 4.8 per cent. Differential smear revealed 62 per cent polymorphonuclears, 4 per cent eosinophiles, 27 per cent lymphocytes, and 7 per cent monocytes. Anisocytosis, and poikilocytosis four-plus and polychromatophilia were also seen. The sickling was four-plus in the wet stain and 70 per cent in the hanging drop. Her weight remained constant at 98 pounds. When the patient was seen in the clinic two months later, her hemoglobin was 60 per cent, red blood count, 2,870,000 with persistent marked sickling in the moist preparation and the white blood count was 11,400.

CASE 3.—E. S., an 18-year-old, colored, gravida i, due on Feb. 6, 1940, first entered the obstetric service on Nov. 16, 1939. She complained of shortness of breath, pain in the left chest, and blood-streaked sputum. Her eyes were frequently "yellow." Recently she had two attacks of left lobar pneumonia, the last one occurring in the second month of this pregnancy, when the sickle-cell anemia was discovered. Upon admission she was acutely ill with a temperature of 100° F. (rectally), pulse 100, respiration 55, and blood pressure 124/82. She appeared frail; her weight was never over 100 pounds, even in late pregnancy. The sclerae were icteric and the pharynx was slightly injected. A soft systolic murmur was present over the apex of the heart and the second pulmonic tones were accentuated. There was a slight enlargement of the heart to the left. Both bases of the lungs had impaired resonance and moist crepitant râles. The uterus was the size of a six and one-half months' pregnancy.

The laboratory study showed that the urine was normal and the blood Kahn was negative. The chest plate showed an enlarged heart with infiltrative changes in both lower lung fields, especially marked on the left side. The blood studies revealed hemoglobin 44 per cent, red blood count 2,860,000 and white blood cells 17,500. Moist coverslip preparations showed 50 per cent sickling. The differential count

hours with delivery of a normal male full-term infant. The puerperal course was uneventful except for the development of a low grade fever up to 101° F. after the sixth post-partum day, with no accountable cause. At the present time she is twenty-two days post partum.

Laboratory findings on the day of admission revealed 3,220,000 red cells and 50 per cent hemoglobin (photoelectric). On the eleventh post-partum day, the red count was 2,730,000, hemoglobin 49 per cent, and white count 29,900. At this time the wet smear again showed sickle cells. There were many abnormalities of color, shape, and size of the red cells and many nucleated forms. She was treated with antianemic diet, iron, and blood transfusions (1,500 c.c.). On the eighteenth day, the red count was 3,910,000 with 50 per cent hemoglobin and 6,900 white cells. Her condition was much improved. At the present time she has sufficiently recovered to be discharged from the hospital. Blood studies on the infant have failed to reveal any sickling tendency up to the present time.

DISCUSSION

Although the etiology of sickle-cell anemia is unknown, it is believed to be a familial disease transmitted by both sexes as a dominant Mendelian characteristic. Gumbiner¹² states that these cases are seen only in the younger age groups, since the majority of persons with active signs of the disease die before they reach thirty years of age, either from the effects of the anemia or from intercurrent infections. This is verified in Table I, summarizing the clinical features of all reported cases of sickle-cell anemia during pregnancy. Here it can be seen that the age of the youngest patient was 18 and that of the oldest was 30, the average age being 22.4. By virtue of the shortened life expectancy of these patients, only 3 of 15 have become multiparas. The viable stage of gestation was reached by 13 of the entire group of 17 mothers. The various theories as to the pathogenesis of this disease, proposed by Jaffe¹³ and by Anderson and Ware,¹⁴ have been discussed by Lash. The essential pathology is found in the spleen, bone marrow, liver, kidneys, and cardiovascular system. Early in the disease the spleen is large and swollen, and later it becomes smaller with marked siderofibrosis. The bone marrow is typically hyperplastic. In all the organs studied a large proportion of the red cells showed sickling. Various authors describe the so-called "abdominal crises" due to the resultant infarction in various abdominal viscera (Yater and Mollari, Campbell¹⁵). Another important terminal pathologic feature is the complicating tendency to infection, especially pneumonia, due to the lowered resistance of the patient because of the severe anemia.

In the 17 reported sickle-cell anemias with pregnancy, there were 5 deaths, 4 of which were subjected to post-mortem examination. "Abdominal crisis" was the terminal cause of death of one patient (Yater and Mollari) and was postulated in another (Lash), although in the latter case an unaccountable postoperative shock prevailed. In the third death the predominant pathology consisted of multiple thrombi, and a complicating pulmonary embolus with multiple infarcts terminally (Page and Silton). Puerperal sepsis claimed the fourth patient six weeks post partum.* The predominant fatal pathology found at autopsy in one of our series (Case 1) was marked hepatosplenomegaly and parenchymatous degeneration of various organs including the heart.

*Disclosed on personal communication with the author. W. P. Killingsworth.

The clinical course was as follows: Two days after admission the temperature dropped to normal, but after five afebrile days the temperature rose to 102.2° F. and spiked irregularly between normal and 104.2° F. The patient coughed considerably at times, but examinations of the chest and x-ray findings were negative. After six days of hyperpyrexia, the temperature gradually but irregularly declined to normal. At this time (the eighteenth hospital day), fetal heart tones disappeared. Two days later she spontaneously delivered a macerated fetus of four and one-half months' size. After the third puerperal day the temperature gradually rose to 102.6° F. and after four days subsided slowly to normal.

On the twenty-sixth hospital day the hemoglobin declined to 24 per cent, and the red count was 1,670,000 and the white count 97,000. At this time she was probably passing through a hematologic crisis. Thereafter the blood picture gradually improved and shortly before her discharge, the hemoglobin was 60 per cent. She was discharged on the twenty-seventh post-abortion day.

CASE 5.—S. P., 20 years of age, colored, gravida i, was first seen in the prenatal clinic on March 25, 1940. Her last menstrual period occurred on Dec. 21, 1939, and she was due to deliver Sept. 28, 1940. She had frequent attacks of rheumatic fever, and joint swelling since five years of age and had been refused life insurance because of an alleged "heart-leak." No abnormal physical findings were noted at first prenatal visit. The Kahn test was negative. The ante-partum clinical course was essentially normal.

She was admitted to the hospital on Sept. 13, 1940, having what proved to be false labor pains. The temperature was 100.6° F. with a pulse of 96. For the first time a diagnosis of rheumatic heart disease with a double mitral lesion and aortic regurgitation was made. Two days after admission the patient went into true labor and after a very short labor delivered a normal female child weighing 7 pounds. This baby had a normal blood picture and no sickling. In the early puerperium the mother had an icteric tinge to her sclerae and the liver was palpable two fingers below the costal margin. Despite a low degree of septic morbidity she made a normal recovery.

The essential laboratory findings were as follows: Two days after delivery the blood picture showed 2,180,000 red cells, 64,000 white cells, and 34 per cent hemoglobin (Sahli). The wet preparation of the blood smear revealed 60 per cent sickling in the red cells. The differential white count was 85 per cent polynucleophiles, 2 per cent metamyelocytes, 1 per cent myelocytes, 3 per cent monocytes, 9 per cent lymphocytes, and one immature cell. It was also observed that the red cells showed anisocytosis, toxicity one-plus, and 87 normoblasts, of which two were stippled. One week later there was marked improvement in the red count and the white count was 18,000; the sickling was markedly decreased.

The treatment administered during the patient's stay consisted of 2 transfusions of 500 c.c. of blood, thiamine chloride 1 c.c. twice daily, liver extract and antianemic diet.

CASE 6.—E. N., 26 years of age, colored, para vi, gravida vii, entered the hospital on Nov. 29, 1940, in labor at term. She had been a patient in the Medical Division of the Cook County Hospital in November, 1939, when she had recovered from pneumonia. At that time sickle-cell anemia had been noted. Her blood count then was 2,400,000 red cells, 36 per cent hemoglobin (photoelectric), and 43,900 white cells. Four nucleated reds and other abnormal forms were noted. She was later followed by the anemia clinic and given iron therapy with good clinical effects. Despite this, low grade anemia prevailed, ranging from 2,860,000 to 4,600,000 red cells. Aside from the anemic picture her prenatal course was uneventful. Previous to this pregnancy, however, she had had frequent rheumatic pains and had been receiving therapy from private physicians for an alleged, but unclassified, anemic condition.

Physical examination revealed no abnormal findings. Two small scars were present on the anterior surface of the left leg. Her labor terminated uneventfully in five

TABLE I. TABLE OF REPORTED CASES IN LITERATURE OF SICKLE-CELL ANEMIA AND PREGNANCY

AUTHORS	AGE	PARA	GRAV.	ESSENTIAL COMPLAINTS	Hb %	R.B.C.	SICKLING	BABY	MOTHER	TREATMENT
Sydenstricker (1924)				Not stated				Sickling in cord blood	Course unknown	Not stated
				Not stated				Sickling in cord blood	Course unknown	Not stated
Yater and Mollari (1931)	25	0	ii	Pains in legs	44	2.57	Active sickling	Six months spontaneous abortion	Died in "abdominal crisis" (autopsy)	Liver and iron
Lash (1934)	21	0	i	Feet swollen; B.P. 145/105	75	3.45	In autopsy sections	Term live baby with sickled red cells	Prolonged labor; died 6 hours post-operatively (autopsy)	Cesarean section
Richter et al. (1934)	21	0	i	Chills and fever on second post-partum day	67	2.17	Sickling noted	Term live baby	Spontaneous delivery; improved later	Oral equine liver
Sharp and Schleicher (1936)	26	0	i	Not stated	25 65	0.90 3.60	Extreme sickling	Term live baby; sickling after 4 months	Normal recovery; improved*	Blood transfusions
Killingsworth and Wallace (1936)		vi	xi	Previous stillbirths; symptoms not stated; four previous abortions		Not stated		Stillbirth; sickle cells in bone marrow	Died six weeks post partum; puerperal sepsis†	Not stated
Lewis (1937)	25	0	iv	Rheumatic heart disease and associated symptoms	40 53	1.60 2.50	50% sickling	Hysterotomy at 4 months	Improved	Diet, iron, liver, hysterotomy

Clinically, certain symptoms and findings are frequently seen. The patients are usually thin and underdeveloped. Four of our patients in this report weighed 100 pounds or less, even when pregnant. The complaints usually consist of frequent attacks of respiratory infections (usually pneumonia), joint and muscle pains (reported 9 out of 14 times), vague abdominal pains with nausea and vomiting, occasional fever, ulcers of the legs, jaundice (usually noticed for many years) and other cardiorespiratory symptoms associated with a severe anemia. The disease is characterized by remissions and exacerbations. During the acute phase of "abdominal crisis" the disease must be differentiated from the acute abdomen (Campbell), rheumatic fever, tuberculosis, syphilis, and obscure anemias (Killingsworth and Wallace).

During pregnancy these patients frequently developed hypertensive or pre-eclamptic toxemia. Of the 13 patients in whom blood pressure recordings were reported, 4 (Lash, Sodeman and Burch, Cases 2 and 3) showed a mild to marked tendency in that direction. The puerperal septic morbidity is frequent observed, and all of our patients had a febrile course.

Roentgenologically, osteoporosis is commonly seen in the long bones with the marrow cavity replaced by radially placed bone formations simulating individual hairs standing on end, while the skull shows increased thickness of the calvarium, loss of continuity of the outer table and replacement of the marrow cavity by altered bone formations (Harden¹⁶).

The diagnosis, of course, rests finally on the blood picture. During the acute episodes of the disease there is a profound anemia, the red count usually being below 2,500,000 with a corresponding decrease in hemoglobin. A moderate to very marked leucocytosis is seen far in excess of what one would ordinarily expect during pregnancy. The red cells are normocytic and normochromic with a tendency toward macrocytosis. There is an increase in reticulocytes, and presence of nucleated red cells with other evidence of marked regeneration. Most of the erythrocytes are sickle shaped, which is best demonstrated on moist coverslip preparations after standing twelve to eighteen hours. Then, practically 100 per cent will assume the abnormal shape characteristic of the disease. With an increase in oxygen tension, there is a tendency of the cells to assume a normal shape, whereas when the oxygen tension is lowered, the cells again become sickled (Hahn and Gillespie¹⁷).

Prognostically, the disease casts a gloomy picture. The majority of patients die before the age of thirty. Pregnancy apparently has an unfavorable effect upon a mother having sickle-cell anemia. In 15 cases where the clinical course of the mother was recorded, 5 did not survive the pregnancy, a mortality ratio of one to three. It has recently come to our attention that at least 2 additional mothers have died sometime subsequent to the publication of their case reports by other authors in the literature (Sharp and Schleicher, and Page and Silton).

The prognosis for the fetus in utero is also unfavorable. From the available data in 15 mothers, 5 (33 per cent) had one or more abortions. These mothers had 37 pregnancies of which only 25 were carried to

viability. Nineteen of these viable babies were born alive, whereas 6 were macerated stillbirths. Among all live births reported in the literature, the blood of at least 8 of the babies developed sickled red cells. Follow-up studies may have revealed a greater number. Lewis comments that the pregnancy caused an exacerbation of the sickle-cell anemia and that the anemia may cause abortions. Sodeman and Burch believe that sickle-cell anemia decreases fertility in the female. Their contention is partially corroborated by the literature which shows that of 15 women of known parity, 10 were pregnant for the first time. Of the remaining 5 women, only 3 had more than 1 live child. The cause of this lack of fertility is not completely understood. The anemia itself may be a cause of lowered fertility and abortion. The presence of anemia for long periods of time, even through the adolescent period into adult life, may have a profound effect upon the reproductive functions. Aside from the mere presence of this anemia, the disease may affect the reproductive function in some other unknown manner (Sodeman¹⁸).

Therapeutically these patients have been subjected to various drugs and surgical procedures. It is significant that all patients who survived pregnancy and labor received intensive antianemic therapy. Seven of these patients received multiple blood transfusions. With the easily available supply of blood transfusions through the blood bank at the Cook County Hospital, this form of therapy has been tested with a measure of success. We believe their improvement is only temporary, however. This improvement is due (according to Josephs¹⁹) to a certain factor present in normal plasma which temporarily maintains normal blood formation and destruction. General supportive measures, such as rest and a diet high in calorie and vitamin content, aid in bringing about improvement. The treatment of any complicating condition, such as intercurrent infections with sulfanilamide or a toxemia of pregnancy, is given as indicated.

SUMMARY AND CONCLUSIONS

1. Six additional cases are added to the existing medical literature on sickle-cell anemia during pregnancy, making a total of 17 cases. Almost one-half of these cases are reported from the Cook County Hospital, which admits annually about 27,000 negroes to its various services and about 3,500 negroes to its obstetric services.

2. An analysis of the reported cases of pregnancy, complicating this type of anemia, has been made, and the pertinent features have been discussed.

3. Sickle-cell anemia during pregnancy is a disease which, while rarely reported at present, is becoming more generally recognized.

4. Most of these cases present themselves in their first pregnancy and only 3 have had more than one child. The exact mechanism of this apparent lack of fertility is not completely understood.

5. Of the 13 cases in which the blood pressure recordings were reported, 4 showed a mild to marked hypertensive toxemia of pregnancy.

6. Patients with this disease have a short life expectancy, being subject to intercurrent infections, especially respiratory, and to the de-

Sodeman and Burch (1938)	23	ii	iii	Axillary pain, dyspnea, vertigo; B.P. 140/80	40 45	2.10 2.67	Marked sickling	Term live baby; all babies had sickled red cells	Normal recovery; improved later	Iron, intramuscular liver
Page and Sifton (1939)	19	0	i	Jaundice, weakness, joint and epigastric pain	42 54	1.86 2.35	Marked sickling	Term live baby	Normal recovery; improved later†	Transfusions (7) iron-copper (Iextron)
	20	0	i	Acutely ill; jaundice; pneumonia	35	1.92	In autopsy sections	Twin 5 mo. pregnancy	Died undelivered (autopsy)	Died 22 hours after admission
Kobak, Stein, and Daro (1940)	22	0	i	Rheumatoid pains; jaundice; acute pneumonia			In autopsy sections	Term macerated stillbirth	Died 6 hours post partum (autopsy)	Sulfapyridine
	30	0	i	Rheumatoid pains; lobar pneumonia; pre-eclampsia; B.P. 160/92	50 68	2.10 3.66	70% sickling	8½ month stillbirth	Recovered from pneumonia post partum	Sulfapyridine, oxygen, blood (4,000 c.c.)
	18	0	i	Lobar pneumonia; pre-eclampsia; B.P. 186/122	44 50	2.86 2.46	50% sickling 66% sickling	7½ month premature live baby; no sickling in R.B.C.	Normal recovery; improved later	Sulfanilamide blood, treatment of toxemia
	18	0	i	Pyelitis	24 50	1.67 2.90	Marked sickling	5½ month abortion; macerated fetus	Improved postabortal	Sulfapyridine, blood, vitamins, diet
	20	0	i	Rheumatic fever and pains; rheumatic heart disease	34	2.18	60% sickling	Term live baby, no sickling	Improved post partum	Blood, vitamins, diet, iron
	26	vi	vii	Previous stillbirth; rheumatic pains; weakness	36 70	2.40 4.60	Moderate sickling	Term live baby, no sickling	Improved post partum	Blood, vitamins, diet, iron

*Died three years later following hysterectomy.

†Additional information by personal communication.

‡Died of pneumonia one and one-half years after publication.

In the first case the patient died of puerperal sepsis six weeks after delivery. It is probable that the sickle-cell anemia weakened her resistance against the infection. Two other patients, the cases of Yater and Mollari and of Page and Silton, presented a syndrome for which the term "abdominal crisis" was coined. The term "abdominal crisis" refers to the sequelae of multiple thrombosis of mesenteric and pelvic veins.

In cases 4 and 5 autopsies were carried out at the Cook County Hospital. In Dr. Lash's case the patient died of "shock" six hours after cesarean section. In the case reported by Drs. Kobak, Stein, and Daro, the patient delivered a macerated baby at term and died six hours later. In both of these cases gross and microscopic findings were strikingly similar. The spleen and liver were enlarged from passive congestion, and the vessels all over the parenchyma were stuffed with red blood corpuscles. Particularly in the liver, the acinar sinusoids were dilated and partially blocked by clumped and coagulated sickled red blood corpuscles, thus obstructing the passage of the portal blood through the liver. Such obstruction in the liver leads to retention and increase of blood in the intestines and to a reduction of the quantity of blood which reaches the heart and circulation in the periphery.

An upset distribution of the peripheral and intestinal blood was first investigated by Fr. v. Mueller in a condition he called "hepatic shock." Hepatic shock which clinically is due to sudden contraction of the portal vein and its branches can be duplicated in animals by injection of histamine. The abnormality of circulation in the two cases of sickle-cell anemia is analogous to the hepatic shock, but the mechanism is different. In hepatic shock the obstruction is due to active contraction of the branches of the portal vein. In sickle-cell anemia, it is a passive blockade, particularly of the acinar sinusoids by clumped red blood corpuscles. If this blockade develops slowly, it leads to stasis and subsequent thrombosis in the mesenteric veins producing an "abdominal crisis." If it develops rapidly, the clinical picture is the same as in hepatic shock.

From these observations of pregnancy in sickle-cell anemia, it seems that the main danger to the patient does not lie in the anemia or in the exhaustion of the bone marrow but in the blockade of the liver. Shortened clotting time and increased fibrinogen rate, hyperinosis, are well-known physiologic pregnancy changes. If these physiologic changes coincide with the pathologically increased tendency for clumping of sickled red blood corpuscles, blockade of the narrow liver sinuses may occur.

DR. FREDERICK H. FALLS.—In this condition we have an increased coagulability of the blood, and an associated increase in the percentage of hypertension. That is significant in view of the idea that thrombosis or vascular accident in the placenta is the underlying factor in the toxemias of late pregnancy.

I would like to raise the question of whether it is wise to give blood transfusions to patients who have this type of blood dyscrasia? Do we know what is going to happen to the blood that we put into a patient who already has a pathologic condition of the blood-clotting mechanism? I am becoming convinced that the indiscriminate use of transfusions in eclamptogenic toxemia is a bad thing, because of certain fatal cases I have seen after the use of blood transfusion.

I should also like to ask about the fate of the baby and, in particular, the time of death of the baby in cases in which stillbirths occurred. This brings up the question of whether cesarean section might not save the baby. We have a condition here which is fatal as far as the mother is concerned, but the baby has a pretty good chance if delivered. If so and if the baby is viable, why not do a cesarean section and insure the life of the baby even though one would take some additional chance on the life of the mother?

DR. KOBAK (closing).—The combination of sickle-cell anemia with pregnancy, while infrequent, is not as rare as the literature would lead one to believe. Since 1924 when Sydenstricker made his publication, and with the six here presented, there will be a total of 17 pregnancies with sickle-cell anemia reported in the literature. When we communicated with these men concerning the subsequent course of the mother, 2 out of 4 replies volunteered information concerning additional cases

generative effects of the severe anemia on the cardiovascular system. At least one-third of the mothers died during or shortly after the pregnancy.

7. This disease has an injurious effect on pregnancy, since one-third of the women had one or more abortions and about one-sixth of the pregnancies terminated in the delivery of macerated stillbirths.

8. At least one-third of the babies were known to have sickling phenomenon.

9. The puerperium is characterized by a tendency toward septic morbidity; all of our patients had a febrile course.

10. The treatment is not specific, various forms of therapy being temporarily effective. Intensive antianemic therapy and repeated transfusions are beneficial.

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185 NORTH WABASH AVENUE

DISCUSSION

DR. RICHARD H. YOUNG.—The anemia of this disease is usually very severe. It is a normocytic normochromic anemia, i.e., there is no change in the size of the red cells or in the hemoglobin content. These points should help to distinguish it from some of the other anemias in pregnancy. Reticulocytes are present during the active phase of sickle-cell anemia. The reticulocyte percentage can, therefore, be used as an index of hemolytic activity. The disease is characterized by remissions and relapses and the patients give a history of periods of ill health and good health throughout their lives.

The sedimentation rate in individuals with sickle-cell anemia is usually normal in character. If there is a high sedimentation rate, there is usually some complication.

In the authors' series there were 5 cases of pulmonary disease. I feel that some of the cases that were diagnosed as pneumonia were probably pulmonary infarctions. In the full paper, I read the complete clinical histories of those patients that died, and I felt the cause of death was probably a pulmonary infarct.

Blood transfusions are the best available type of treatment. The use of iron and liver is not on a sound basis. There is no loss of iron to the outside, and, therefore, no deficiency of iron. There is no macrocytic anemia, so you would not expect liver to be effective.

DR. WALTER SCHILLER.—An analysis of these cases may throw some light on the problem of the way sickle-cell anemia complicates pregnancy.

The procedure about to be described is not entirely original, but rather a composite one, in which an attempt is made to incorporate all the better features of the methods already known with some variations which are original.

PROCEDURE

Three plates of the pelvis are taken routinely, a horizontal anteroposterior, a horizontal lateral, and a 45 degree angle exposure of the subpubic arch and side walls. A Potter-Bucky diaphragm and a medium-sized cone are used. No special equipment is necessary except for a metallic ruler which has notches 1 cm. apart. This is placed between the buttocks and partially between the inner surfaces of the thighs for support when taking the lateral exposure.

TABLE I. TECHNIQUE

	KILOVOLT PEAK	MILLI- AMPERES	TIME SEC.	DISTANCE INCHES	TUBE CENTERED	REMARKS
AP	65-75	30	5	30	Midline 8 cm. back of symphysis.	Keep thighs together. Tilt pelvis 45° with pillow doubled in small of back
LAT.	80-90	30	15-40	30	Over hips	Be sure that pelvis is not rotated. Slightly flex thighs. Thighs together
45°	75	30	5	25	Aim at subpubic arch at 45° angle	Flex and abduct thighs so that subpubic angle can be seen. Withdraw pillow

MEASUREMENT AND INTERPRETATION OF THE FILMS

Lateral Plate.—Inasmuch as the metallic ruler lies in the midline, its image on the film will be distorted (enlarged) in the same proportion as all the anteroposterior measurements taken in this plane. To find the true measurement of any anteroposterior diameter, therefore, one needs only to measure the distance between the anterior and posterior landmarks of any plane (inlet, midplane, or outlet), transpose the distance on the image of the ruler on the plate, and then read the true measurement.

To obtain the transverse diameters of the pelvic planes, one should measure the distance between the recognized transverse landmarks of each plane directly on the anteroposterior plate. Inasmuch as the transverse planes of the inlet, midplane, and outlet lie at different distances from the x-ray tube, the degree of distortion of each is different. If, however, the distance from the plate to the transverse plane to be measured is known, the degree of enlargement is easily determined and a true accurate measurement is obtained.

In order to ascertain how far the transverse plane measured is from the table top, the lateral plate is consulted. A baseline is drawn parallel to the film edge that touches the most lateral border of the sacrum. This represents the table top if the patient were lying flat on her back. In order to find how far the plane is from the table top, one need only measure the distance from the plane to the baseline and read the result directly from the ruler image on the plate. If Table II is then consulted, using both the table-top-plane measurement and the transverse measurement of the image on the anteroposterior plate, the true transverse measurement is then determined.

INTERPRETATION OF PLATES

For the sake of clarity, the interpretation of a typical set of plates will be discussed in detail:

1. *Measurements.*—On the lateral plate, a line is drawn from the upper border of the symphysis to the midpoint on the sacrum where the two white ileopectineal

which came to their attention. These men stated that they had now seen 10 additional cases of pregnancy with sickle-cell anemia.

I believe it was our awareness of this anemia that made it possible for us to diagnose our 6 cases during the past two years. Because of this awareness, and the prompt diagnosis, the therapy that was given was helpful in carrying 5 out of 6 of these women past the puerperium. I have a feeling that possibly some of our puzzling deaths that heretofore occurred among negro patients might have been an undiagnosed sickle-cell anemia.

In answer to the question raised by Dr. Falls, we have found that without a doubt transfusions have been very helpful. While one may consider the possibility of some unfavorable action, the sum total was satisfactory.

Examination of the babies' blood showed one out of three with sickle-cell phenomena. In one case this sickle-cell phenomenon did not appear until the fourth month. We do not know how many of these babies may later develop a sickle-cell anemia.

Concerning the use of cesarean section and its value, I cannot answer that question. There is a possibility as suggested by Dr. Schiller that it may throw the patient into shock or crisis. Our policy has been to treat these patients medically and with transfusion therapy; we only used obstetric procedures when the usual indications called for them.

A SIMPLE METHOD OF X-RAY PELVIMETRY

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IT IS not the purpose of this paper to justify the use of x-ray pelvimetry in the scientific practice of obstetrics. This has been ably done by Thoms, Caldwell, Moloy, Steele, and others. Its intention is to describe a method which can be used readily by every physician who handles obstetric cases.

The many excellent methods of x-ray pelvimetry available today are extremely complicated, either from the standpoint of taking the films, or in the interpretation of the finished x-ray plate. They either include complicated tube shifts, grids, stereoscopically taken films, complex mathematical calculations, or some other factor which may confuse the average practitioner, so that he cannot master and readily adopt this procedure.

There are comparatively few today who are able to read a pelvic roentgenogram. This is easily proved by the fact that usually one man on the obstetric staff of even the larger hospitals is assigned to the interpretation of pelvic x-rays. Why should the methods used be so complex that many obstetricians and the great majority of general practitioners cannot interpret the plates accurately?

It was our purpose to find some simple method which could be used generally in private practice. We tried to fulfill the following conditions: (1) No extra expensive equipment should be necessary for either taking or interpreting the pictures; (2) reading of the plate should not require special training; (3) measurements should be between set points, and no differences should exist between different examiners because of ocular variations; (4) the technique of the taking of the x-ray exposures should be simple; and (5) the method should be accurate.

TABLE II.* MEASUREMENT TO BASELINE. LATERAL PLATE

CENVI- METERS	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
4.0	3.6	3.5	3.4	3.4	3.4	3.3	3.3	3.2	3.2	3.1	3.1	3.0	3.0	2.9	2.9
4.5	4.1	4.0	3.8	3.8	3.8	3.7	3.7	3.6	3.6	3.5	3.5	3.4	3.4	3.3	3.3
5.0	4.5	4.4	4.2	4.2	4.2	4.1	4.0	3.9	3.9	3.8	3.8	3.7	3.7	3.6	3.6
5.5	5.0	4.9	4.6	4.7	4.6	4.6	4.5	4.4	4.3	4.2	4.2	4.1	4.1	4.0	4.0
6.0	5.4	5.3	5.1	5.1	5.0	4.9	4.9	4.8	4.7	4.6	4.6	4.5	4.4	4.3	4.3
6.5	5.9	5.8	5.5	5.5	5.5	5.3	5.3	5.2	5.1	5.0	5.0	4.9	4.7	4.7	4.6
7.0	6.3	6.2	5.9	5.9	5.8	5.7	5.7	5.6	5.5	5.4	5.3	5.2	5.0	5.0	4.9
7.5	6.8	6.6	6.5	6.4	6.3	6.2	6.1	6.0	5.9	5.8	5.7	5.6	5.5	5.4	5.3
8.0	7.2	7.0	6.9	6.8	6.7	6.6	6.5	6.4	6.3	6.2	6.0	6.0	5.9	5.8	5.7
8.5	7.6	7.5	7.4	7.2	7.1	7.0	6.9	6.8	6.7	6.6	6.5	6.4	6.3	6.2	6.1
9.0	8.0	7.9	7.6	7.6	7.4	7.3	7.3	7.2	7.0	6.9	6.9	6.8	6.6	6.5	6.4
9.5	8.5	8.4	8.3	8.1	7.9	7.8	7.7	7.6	7.5	7.4	7.3	7.2	7.0	6.9	6.8
10.0	8.9	8.8	8.6	8.6	8.4	8.3	8.2	8.0	7.9	7.8	7.6	7.5	7.4	7.2	7.1
10.5	9.4	9.3	9.0	9.0	8.9	8.7	8.6	8.4	8.3	8.2	8.0	7.9	7.8	7.7	7.4
11.0	9.8	9.7	9.4	9.4	9.3	9.1	9.0	8.8	8.7	8.5	8.4	8.2	8.1	7.9	7.8
11.5	10.3	10.1	9.9	9.9	9.7	9.5	9.4	9.2	9.1	8.9	8.8	8.6	8.5	8.3	8.2
12.0	10.7	10.5	10.4	10.3	10.1	9.9	9.8	9.6	9.5	9.3	9.2	9.0	8.8	8.6	8.5
12.5	11.2	11.0	10.9	10.7	10.5	10.3	10.2	10.0	9.9	9.7	9.6	9.4	9.2	9.0	8.9
13.0	11.6	11.4	11.3	11.1	10.9	10.7	10.6	10.4	10.3	10.1	10.0	9.8	9.6	9.4	9.2
13.5	12.1	11.9	11.7	11.5	11.4	11.2	11.0	10.8	10.7	10.5	10.3	10.1	10.0	9.8	9.6
14.0	12.5	12.3	12.1	11.9	11.8	11.6	11.4	11.2	11.0	10.8	10.6	10.4	10.3	10.1	9.9
14.5	13.0	12.8	12.6	12.4	12.2	12.0	11.8	11.6	11.4	11.2	11.0	10.8	10.7	10.5	10.3
15.0	13.4	13.2	13.0	12.8	12.6	12.4	12.2	12.0	11.8	11.6	11.4	11.2	11.0	10.8	10.6
15.5	13.9	13.7	13.5	13.3	13.1	12.8	12.6	12.4	12.2	12.0	11.8	11.6	11.4	11.2	11.0
16.0	14.3	14.1	13.9	13.7	13.5	13.2	13.0	12.8	12.6	12.4	12.2	12.0	11.8	11.6	11.4
16.5	14.8	14.5	14.3	14.1	13.9	13.6	13.4	13.2	13.0	12.8	12.6	12.4	12.2	12.0	11.8
17.0	15.2	14.9	14.7	14.5	14.3	14.0	13.8	13.6	13.4	13.2	13.0	12.8	12.6	12.4	12.2
17.5	15.7	15.4	15.2	14.9	14.7	14.5	14.3	14.0	13.8	13.6	13.4	13.2	13.0	12.8	12.5
18.0	16.1	15.9	15.6	15.3	15.1	14.9	14.7	14.4	14.2	13.9	13.7	13.5	13.3	13.1	12.8

*This table is corrected for the additional 5 cm. from the table top to the plate.

The corrected figures are obtained, using the geometric theorem "In similar triangles, the base is proportional to the altitude."

The posterior sagittal of the outlet is measured from the midpoint between the tuberosities to the end of the sacrum, and this again is read directly by transposing the measurement on the ruler on the film. Thus, the diameters of the obstetric conjugate, posterior sagittal of the inlet, midplane, and outlet are obtained.

In order to obtain the transverse measurements, one simply measures with a centimeter ruler on the anteroposterior plate the distance between the widest points of the ileopectineal lines (inlet), the interspinous diameter (midplane), and the intertrochanteric distance (outlet). These must be corrected for distortion.

TABLE III. FRENCH HOSPITAL (HISTORY CHART)

NAME	HISTORY NO. DR. X-RAY NUMBER
1. Inlet	
a. Measurement of obstetric conjugate 9.5-11.5 cm.	
b. Measurement of posterior sagittal 4-5 cm.	
c. Measurement of transverse 12-13 cm.	
d. Shape of posterior segment	{ Gynecoid Anthropoid Android Platypelloid
e. Shape of anterior segment	{ Gynecoid Anthropoid Android Platypelloid
f. Symmetry	
2. Midplane	
a. Measurement of interspinous diameter 9.5-10.5 cm.	
b. Measurement of posterior sagittal diameter 4.5-5.5 cm.	
c. Prominence of spines.	
3. Outlet	
a. Measurement of intertrochanteric diameter 9-11 cm.	
b. Measurement of posterior sagittal of outlet 7.5-9 cm.	
4. Depth of Pelvis 90-100 millimeters.	
5. Length of sacrum 11-13 cm.	{ Long Average Short
6. Sacral curve	{ Straight Average Marked
7. Inclination of sacrum (normal 90°)	
8. Width of sacrum	{ Wide Average Narrow
9. Subpubic angle (normal 80-90°)	{ Wide Average Narrow
10. Shape of arch	{ Roman (round) Normal Gothic (angular)
11. Sidewalls of pelvis	{ Converge Straight Divergent
12. Lateral bore	{ Converge Straight Divergent
13. Apex sacrosciatic notch	{ Wide Average (about 3 cm.) Narrow
14. Base of sacrosciatic notch wide	{ Average (4-5 cm.) Narrow
15. Baby	{ Position Engagement Flexion Station Abnormality

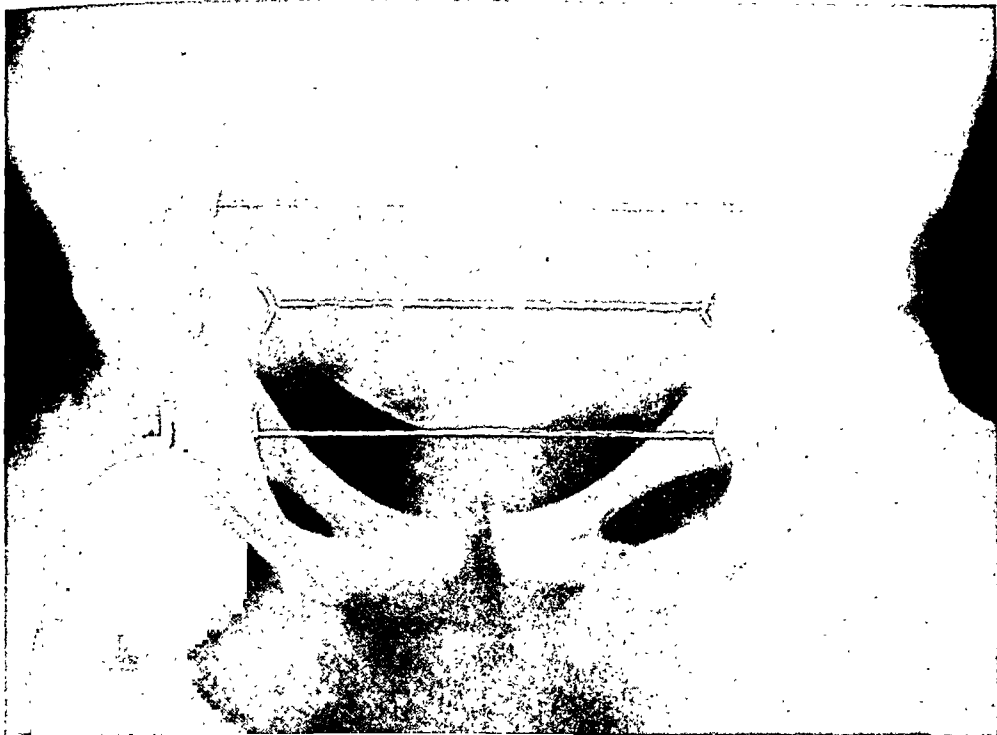


Fig. 2.—Anteroposterior view of the pelvis. *H-J*, Widest transverse diameter of the inlet; *K-L*, interspinous diameter of the midplane; *M-N*, transverse diameter of the outlet. Also observe the shape of both the anterior and posterior portions of the inlet, its symmetry, and the prominence of the spines.



Fig. 3.—Forty-five degree angle view of the pelvis. Observe the direction of the side walls, the shape of the subpubic arch, the width of the subpubic angle, and the depth of the pelvis.

the factor which causes many to make extravagant claims for this procedure. The pelvis is only one factor in labor. The parity of the woman, her race, age, emotional stability, the amount of sedation, the character of the uterine contractions, the dilatation of the cervix, obstructing tumors, the size of the baby, its position, flexion, etc., all are factors which determine the final outcome.

I wish to express my sincere gratitude to Dr. Claude Heaton and Dr. E. M. Claiborne for their help and cooperation in this work.

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115 EAST FIFTY-THIRD STREET

THE NAEGELE PELVIS*

THE OBSERVATION OF THREE CASES AND A COMMENTARY

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ONE hundred and one years ago Franz Carl Naegele¹ gave to the world his celebrated treatise on the obliquely contracted pelvis. Since that time, the name of this particular type of pelvic deformity has memorialized the author of this medical classic, for it is known as "The Naegele Pelvis."

Naegele defined the deformity as a "pelvis contracted in one of the oblique diameters with complete ankylosis of the sacroiliac synchondrosis on one side, combined with imperfect development of the sacrum and os innominatum on the same side." At the time of his writing the author observed that the deformity had never been recognized in the living body. Without the aid of roentgenology, it may be stated that much of the same difficulty of diagnosis that Naegele experienced obtains today, as witnessed by the cases here reported.

The object of the present communication is to place on record the recent observation of three cases and to emphasize the opinion that the deformity probably is not one of the extreme rarity usually assumed. Williams, in 1926,² stated that probably less than 100 instances have been described in the literature.

*This study was made possible through the Clinical Research and Teaching Fund of Yale University School of Medicine.

Therefore, on the lateral plate, the baseline previously described is drawn parallel to the film edge, touching the most lateral border of the sacrum. To determine the distortion of the inlet, the distance from the junction of the posterior and anterior sagittal of the inlet to the baseline is measured, using the ruler image on the plate. Then by simply consulting Table II the true undistorted transverse measurement is given. To correct for the distortion of the midplane, the distance from the midpoint between the spines to the baseline is measured, and again the same table is consulted. For the transverse of the outlet, measure the distance from the midpoint between the tuberosities to the baseline with the ruler image, and then find the corrected transverse measurement on the chart.

2. *Architecture of the Pelvis.*—While pelvic measurements are important, they do not tell the entire story. The pelvic architecture must be studied very carefully in all three plates. The 45 degree angle exposure is especially valuable in studying the subpubic angle and the side walls (Table III).

Table III is given so that the inexperienced physician may have some system of evaluating the pelvis, and some basis for his judgment of its capacity. A set of average normal measurements are given. If there is any marked variation, it is advisable for the physician to consult with a qualified obstetrician with greater experience, who on the basis of his past experience can better evaluate the pelvic architecture and measurements.

The measurement of the head, or fetal cephalometry, has not been particularly successful in our hands, regardless of the technique used. Communications with other clinics have disclosed similar difficulties.

The reason for the difficulty is clear. First, the frontooccipital is the only diameter that we are able to measure, and this is not the diameter that engages. Next, we compare this with the smallest pelvic diameter and do not take into account the fact that compensatory space may exist either laterally, anteriorly, or posteriorly. Finally, we do not know how much molding the head will undergo as it comes through the pelvic canal. Goodwin's work showing that the long oval head flexes and molds well while the round head does not, definitely contributes toward the solution of this problem. Finally, the mechanism of labor, the condition of the cervix, the intensity of the pains, and many other factors must be considered.

We, therefore, feel that actual measurements of the head may be misleading. If the pelvis is average in measurement with good architecture, a 7- to 8-pound baby should deliver spontaneously. If it is larger, it is capable of accommodating even a larger baby. If it is smaller, a 5- to 7-pound baby will deliver spontaneously. With good pelvic construction, every woman with an average size baby who has an obstetric conjugate of 9 cm. is entitled to the chance of delivery from below. The great majority have no difficulty. We consider an obstetric conjugate of 8 cm. an absolute contraction.

Routine pelvimetry for all primiparas and all multiparas with previous difficult labors will soon be a routine procedure in scientific obstetrics. It is hoped that with the simplification of methods and wider adoption of this procedure, the high incidence of cesarean section will be reduced because of misconceptions concerning the size of the pelvis. We also hope that with this procedure, the abnormal pelvis will be more universally recognized, and adequate measures taken so that proper facilities are available when a difficult delivery is anticipated. When a diagnostic help to the doctor is harmless to the patient, it should absolutely be used whenever possible. If absolute cephalopelvic disproportion is seen, babies will not be subjected to tests of labor which result in birth injuries.

In conclusion, a note of warning must be given. X-ray pelvimetry is not a panacea, but it can be of great value if its limitations are appreciated. It is merely a diagnostic aid. Inexperience is usually

pregnancy and noted that the inferior pelvic strait was abnormal and referred the patient for roentgen pelvimetry. The report of the roentgen examination on Jan. 4, 1940, states that "The pelvic contour is that of a Naegele type with obliquity and deformity on the right" (Fig. 2). The patient's prenatal course was uneventful



Fig. 1.—Case 1. Anteroposterior roentgenogram.



Fig. 2.—Case 2. Anteroposterior roentgenogram.

until she was seen on April 18, 1940, when the relatively large size of the abdomen suggested the presence of multiple pregnancy. Two weeks later this impression was confirmed by roentgen examination. Toward the end of pregnancy the patient's blood pressure began to rise, her weight to increase rapidly, and the urine showed albumin. From May 2 to June 11 the pressure rose from 148/88 to 166/92, and on

The *first* case presented I have previously recorded,³ but a brief description is also of interest in this communication. The patient, a woman of 33 years, of Irish descent, gave no history of serious disease in childhood. The menstrual history was negative and no pregnancies had occurred. In 1928 the left kidney was removed in a local hospital, the indication being pyelitis. The removed specimen showed kidney deformity with double pelvis and double ureter. The patient was first seen in the New Haven Hospital the following year. From that time on she has been seen at various intervals, her chief complaint usually being pain in the left lower abdominal quadrant. From 1932 to 1938, 8 pelvic examinations were made by 6 individuals. No note is made following these examinations as to the presence of pelvic deformity. Examinations failed to reveal any definite cause for her discomfort, and in January, 1938, a flat abdominal roentgenogram was made (Fig. 1). The report showed scoliosis of the left dorsal spine and deformity of pelvis with associated sclerosis in region of left sacroiliac articulation; in other words, a Naegele type pelvis. Examination under anesthesia revealed no gynecologic pathology. The external measurements follow:

Interspinous diameter	23.5 cm.
Intercristal diameter	25.0 cm.
Intertrochanteric diameter	29.0 cm.
Right oblique diameter	18.5 cm.
Left oblique diameter	17.25 cm.
External conjugate diameter	17.25 cm.

Pelvic measurements as determined by roentgen pelvimetry:

Anteroposterior diameter of inlet	9.5 cm.
Greatest transverse diameter of inlet	10.0 cm.
Left oblique diameter	11.0 cm.
Right oblique diameter	8.25 cm.
Interischial spinous diameter	6.25 cm.
Intertuberal diameter	10.0 cm.
Posterior sagittal diameter of outlet	5.25 cm.
Height of pelvis	9.25 cm.

Laterally the pelvis showed a male type of sacrosciatic notch, and the sacrum showed an essentially normal curve from above downward on its anterior surface. The pelvic and iliac portions of the terminal length are as follows:

Right side	{ Pubic portion	6.0 cm.
	{ Iliac portion	5.5 cm.
Left side	{ Pubic portion	6.75 cm.
	{ Iliac portion	4.5 cm.

The external appearance of the patient was not unusual, scoliosis not readily noticeable, and the patient does not walk with any noticeable limp.

The *second* case is that of an Italian woman, aged 38 years, first seen in our clinic in December, 1939. She was then in her fourth pregnancy. Her first pregnancy in 1925 was ended in delivery by forceps in a local hospital of a male child, 7 pounds 10 ounces, now living and well. The second pregnancy in 1928 terminated in spontaneous delivery of a female child, 7 pounds 14 ounces, now living and well. In 1931 she was delivered at home by a local physician of a child which is claimed to have weighed over 8 pounds. This child is said to have suffered a birth injury. It died at the age of thirty-one months from infection, according to the mother's statement.

The patient's past history revealed nothing of importance as far as the pelvic deformity was concerned. Her expected confinement was July 7, 1940. In reviewing this patient's dispensary history, it was found that she visited the clinic in 1934 for "pains in the lower abdomen." At that visit and on four subsequent visits, a vaginal examination was done. These examinations were performed by four different individuals and no mention of pelvic deformity appears on the record. On Dec. 26, 1939, she again presented herself, as noted above, in her fourth pregnancy. At that time a vaginal examination was done by Dr. DeWitt Dominick, who confirmed the

which is living and well. The second pregnancy ended in the stillbirth of a 9.5 pound infant which was delivered with forceps. The expected date of the present pregnancy is April 4, 1941, and except for some varicosities on both legs and the deformity of the pelvis the pregnancy seems to be uncomplicated.* The past history is of interest because of a history of osteomyelitis during the first three years of life, accounting for numerous scars due to incisional drainage in the region of the left hip.

On her first visit to our clinic on Oct. 1, 1940, she was examined vaginally by my associate, Dr. Clair B. Crampton, who noted that the pelvis presented deformity and he referred the patient for roentgen pelvimetry. The roentgen findings showed the presence of a typical Naegele pelvis with the deformity on the right side (Fig. 3). The external measurements were as follows:

Interspinous diameter	22.5 cm.
Intercrestal diameter	24.25 cm.
Intertrochanteric diameter	29.0 cm.
Right oblique diameter	17.75 cm.
Left oblique diameter	15.0 cm.
External conjugate	17.5 cm.

Pelvic measurements as determined by roentgen pelvimetry:

Anteroposterior diameter of inlet	11.0 cm.
Greatest transverse diameter of inlet	10.0 cm.
Left oblique diameter	9.4 cm.
Right oblique diameter	11.8 cm.
Interischial spinous diameter	8.1 cm.
Intertuberal diameter	8.2 cm.
Posterior sagittal diameter of outlet	9.0 cm.
Height of pelvis	9.25 cm.

In addition to the roentgenometric findings, the films showed some destruction of the crest of the ilium on the left or the side opposite to the pelvic deformity. This destruction is characteristic of that caused by osteomyelitic disease.

Laterally the pelvis showed a femal type of sacrosciatic notch, and the sacrum was convex from above downward on its anterior surface, somewhat characteristic of the rachitic sacrum. The pelvic and iliac portions of terminal length were as follows:

Right side	{ Pubic portion	6.5 cm.
	{ Iliac portion	5.5 cm.
Left side	{ Pubic portion	6.3 cm.
	{ Iliac portion	7.0 cm.

Except for the scars on the left side, the external appearance of the patient is not unusual and the scoliosis is not marked. The patient does not walk with a noticeable limp.

COMMENT

In discussing the origin of this type of pelvic deformity Naegele wrote, "I confess that my original opinion about it, namely that the deformity originates neither from external force nor from disease but by a deviation in the original development, appears the most probable." Naegele gave his reasons for this opinion, which I quote in part as follows:

"The intimate and complete fusion of the os sacrum and os ilium includes the inner structure of the bones as well as its external appearance. There is no trace of growing together of formerly separated parts in the region of the synostosis. . . . The os sacrum and os innominatum form one bone . . . if our fusion of the os

*This patient was delivered by cesarean section, March 28, 1941. The child weighed 3,890 Gm.

June 18 she was admitted to the hospital for observation. Forty-eight hours later the membranes ruptured spontaneously and labor started. She was delivered of male twins without difficulty after a seven-hour labor, and the weight of the children was 2,830 and 2,725 Gm. The puerperium was uneventful and the patient was discharged on the twelfth day post partum. The blood pressure on discharge was 110/82. Before the patient left the hospital roentgen examination of the urinary tract by pyelography was performed. No gross abnormalities were noted. The external measurements of Case 2 follow:

Interspinous diameter	26.0 cm.
Intercristal diameter	29.0 cm.
Intertrochanteric diameter	32.0 cm.
Right oblique diameter	23.0 cm.
Left oblique diameter	19.75 cm.
External conjugate diameter	20.5 cm.

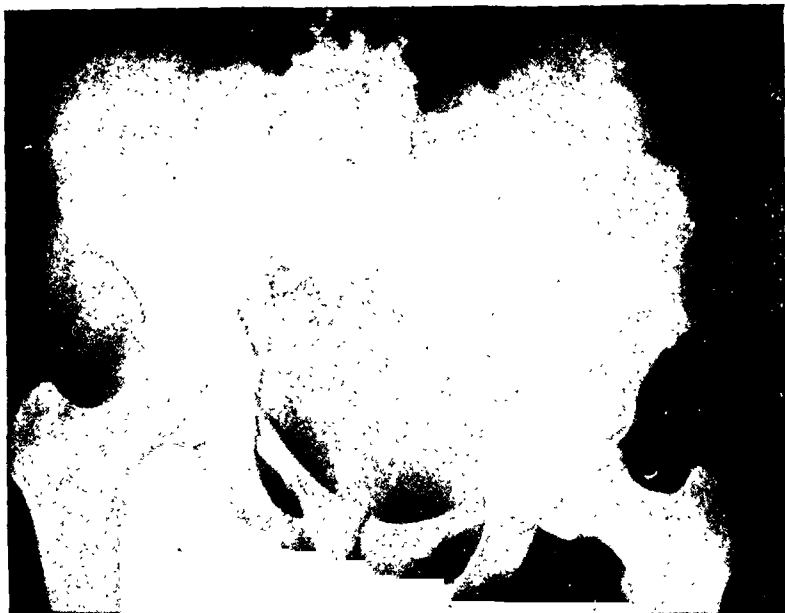


Fig. 3.—Case 3. Anteroposterior roentgenogram.

Pelvic measurements as determined by roentgen pelvimetry:

Anteroposterior diameter of inlet	12.0 cm.
Greatest transverse diameter	10.0 cm.
Left oblique diameter	9.5 cm.
Right oblique diameter	12.4 cm.
Interischial spinous diameter	7.1 cm.
Intertuberal diameter	8.5 cm.
Height of pelvis	9.8 cm.

Laterally the pelvis shows a male type of sacroscliotic notch and the sacrum from above downward shows a slight abnormal displacement forward of the lower half. The pelvic portions of the terminal length are as follows:

Right side	{ Pubic portion	6.3 cm.
	{ Iliac portion	8.0 cm.
Left side	{ Pubic portion	8.3 cm.
	{ Iliac portion	6.0 cm.

The *third* case, now under observation in our prenatal clinic, is that of a 28-year-old white American who is pregnant for the third time. The first pregnancy in 1935 was terminated in a local hospital by forceps, and a 7.5 pound child delivered,

the true condition was suspected. With regard to these examinations it is fair to state that only within a comparative recent time has our attention been specifically directed to the obstetric importance of mid-plane contractions. In any event, it is obvious that the diagnosis may not be readily apparent without the use of roentgen investigation.

The absence of obvious external deformity and change in gait are also contributory to the obscurity of diagnosis. However, variations in the height of the iliac crests and an accompanying scoliosis are suggestive findings. The transverse diameter of the outlet is always diminished, usually markedly, so that there is a definite sense of constriction in examining vaginally. Laterally the pelvic side wall on the affected side is readily felt on vaginal examination and is found to be displaced toward the body midline. A simple anteroposterior roentgenogram always settles the diagnosis.

CONCLUSION

The finding of three Naegele pelves within two years in the relatively small material of our clinic suggests that this type of pelvis may not be one of extreme rarity. The history of full-term pregnancies successfully delivered in the second and third case also suggests that such a pelvis may easily remain unrecognized in the ordinary course of events. The potential difficulties which may result obstetrically in such pelvis point out the importance of a definite diagnosis in each case. The importance of the routine procedure which we have carried out for the past six years, namely that of performing roentgen pelvimetry on every primigravid woman, again becomes obvious.

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There were 74 patients under 16 years of age among 133,361 deliveries during the years 1931 to 1938 in 23 municipal maternity units in London, England. The maternal mortality was nil, and there were 2 stillbirths and 3 neonatal deaths. The labors were, with few exceptions, short and unusually easy. There was a slight increase over the normal rate for these hospitals of forceps, surgical inductions, and puerperal morbidity. Complications, especially during the third stage, were rare. There was no evidence that maternity had produced excessive nervous or mental strain, and no case of mental or nervous breakdown has been traced.

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sacrum and os ilium should be considered as a synostosis acquisita as a consequence of inflammation or of pressure, etc., it could hardly be found as complete, as uniform as we find it in all pelves of our class. . . . The truly striking resemblance of these pelves to one another in all important characteristics is so obvious. . . . Whoever has seen a series of such specimens must have the idea that there is a common cause for this deformity. Does not identity of the effect speak for the identity of the cause? . . . In none of the cases could a disease or an exterior force be made responsible for the deformity. All cases which have come to my knowledge occurred in young people who had previously been healthy."

However, in spite of Naegele's impressive argument, Thomas of Leyden,⁴ in 1860, stated that in certain cases inflammatory disease rather than congenital defect was responsible for the condition. At a later date Breus and Kolisko⁵ went further and stated that the condition was always the result of inflammatory disease and that the history and presence of cicatrices would substantiate this fact. In 1929, Williams⁶ concluded that this latter opinion may not apply to the individual case. In his case, as in Reinberger's⁷ reported in 1933, an embryonic defect was the only solution that explained the deformity. In addition to the pelvic deformity in the latter's case, there were deformities of the lower extremities and supernumerary digits of both upper and lower extremities, and the genital tract showed a uterus septus with double cervix and double vagina.

In 1917, Berry Hart⁸ summarized his views on this subject as follows: "The true Naegele and Robert pelves have not had a previous ostitis with resulting ankylosis in the region of the sacroiliac joints, followed by disturbed weight transmission. The pseudo-Naegele and pseudo-Robert pelves have had a previous ostitis in these regions, and there the synostosis and atrophy are the result of this. The forms of the Naegele and Robert pelves are the result of polar losses of the size elements of the alae sacri and innominate bones, due to maturation of the sperm- and germ-cells. In these the loss of the alae sacri and innominate determinants has occurred, a great rarity, more often a unilateral loss (Naegele) than a bilateral one (Robert). The sacroiliac ankylosis is due to the fact that by such losses (bony elements and joint elements) the part remaining, imperfectly developing, becomes ankylosed. As this is a germ-plasma change, and multiplication of the reduced elements occurs, it may be transmitted."

It is of interest to note that Bluntschli⁹ in 1911 described the occurrence of this type of pelvic deformity in the monkey (*Macacus cynomolgus*) and that earlier in 1878 Thomson¹⁰ exhibited the skeleton of a wombat (*Phascalomys*) in which the same unilateral sacral changes were present.

The association of this deformity with evidences of maldevelopment in other parts of the same individual certainly gives some weight to the congenital nature of its origin. In Case 1 of the present group, in Reinberger's case, and in Riviere and Riviere's case, the coexistent malformations were those definitely associated with the urogenital system. In the latter instance reported in 1923,¹¹ there was absence of the half of the uterus, uterine horn, and ovary, all on the same side as the bony deformity. A recent personal communication from Dr. N. J. Eastman reports a case of Naegele pelvis in a patient in whom nephrectomy was performed for renal tuberculosis, occurring on the same side as that of the deformity.

The diagnosis of Naegele pelvis in the living being presents an interesting topic for discussion. In many instances, as in the cases here presented, knowledge of the condition is unknown until for one reason or another a roentgenogram of the pelvis is made. In my first case and in Dr. Eastman's case, the deformity was discovered during a urologic investigation. In the second and third cases of the present group, both individuals had given birth to children and had been subjected to numerous vaginal examinations by presumably competent observers before

TABLE II. POSSIBLE PREDISPOSING FACTORS IN 155 CASES OF CORD PROLAPSE

POSSIBLE PREDISPOSING FACTOR	NO.	INCIDENCE PER CENT	FETAL MORTALITY	
			DIED	PER CENT
Abnormal bony pelvis	28	18.1	13	46.4
Abnormal placentations	9	5.8	7	77.7
Polyhydramnion	9	5.8	5	55.5
Infants over 9 pounds birthweight	24	15.5	15	62.5
Infants under 6 pounds birthweight	34	21.9	21	61.8
Premature infants	32	20.6	23	71.7
Twins	10	6.5	2	20.0
Abnormal fetus, hydrocephalic	1	0.7	1	100.0
Abnormal lies and presentations	61	39.4	28	46.0
Transverse lies	13	8.4	7	53.8
Longitudinal lies	48	30.9	21	43.7
Cephalic presentations	11	7.2	7	63.6
Compound	9	5.8	6	66.7
Face	2	1.3	1	50.0
Sacral presentations	37	23.9	14	37.8
Double footlings	18	11.6	8	44.4
Single footlings	14	9.0	4	28.6
Full breeches	2	1.3	1	50.0
Frank breech	1	0.7	0	0.0
Unclassified	2	1.3	1	50.0

Overlapping exists in the above groups, and conversely some cases fall into no group. Fifty-seven occipitoanterior and 37 occipitoposterior positions, with fetal mortalities of 57.7 and 43.2 per cent, respectively, are not included in this table; nor are parity figures, cited in the text.

reserve as a possible eventuality. During the first stage of labor, while the head was unengaged, the fetal heart tones disappeared. Eleven hours later she delivered a stillborn fetus with a prolapsed cord. She was pregnant again the following year, and bore a fetus larger than her first. Stereoroentgenologic examination near term disclosed an android pelvis with a high posterior vertex. After two hours of labor, while the head was still unengaged and the cervix dilated only 2 cm., the fetal heart tones became irregular. The patient was placed in the Trendelenburg position, prepared, and delivered by the abdominal route. When the uterus was opened, the umbilical cord was found "below the head, compressed against the brim of the pelvis." A living 8 pound 2 ounce infant was obtained.

Multiparity is commonly said to favor cord prolapse.^{5, 6} This study embraces 14,181 primiparous and 22,592 multiparous confinements, of which 58 and 97, respectively, were complicated by prolapse of the cord. The percentage incidence of cord prolapse in these two groups, 0.41 for primiparas and 0.43 for multiparas, discounts at least in this study the etiologic importance of multiparity. Furthermore, the fetal mortality percentages, 51.7 and 48.5, respectively, are of almost identical order.

Table III, which analyzes the precipitating causes of cord prolapse, reveals that any pelvic manipulation or even the patient's struggles under anesthesia may act as an initiating factor. Artificial rupture of the membranes was performed in 27 cases with living infants on the following indications: prolonged labor 12, induction of labor 7, control of hemorrhage 4, and to expedite delivery of the second twin 4. Insertion of a Voorhees' bag initiated cord prolapse once, while its expulsion was followed by the mishap 4 times. Manual rotation of the head pre-

PROLAPSE OF THE UMBILICAL CORD

ANALYSIS OF ONE HUNDRED AND FIFTY-FIVE CASES

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ANALYSIS of 155 cases of cord prolapse occurring at the Providence Lying-in Hospital during the fifteen years preceding July 1, 1940, brings out several facts at variance with accepted concepts. For the sake of brevity, the essential statistics of this review will be presented in tabular form, and only points of particular interest will be discussed.

INCIDENCE

Cord prolapse occurred 155 times in 36,773 consecutive viable confinements, an incidence of 0.42 per cent. Comparison of this figure with others (Table I) suggests that a general reduction in the incidence of this mishap is taking place.

TABLE I. INCIDENCE OF CORD PROLAPSE

YEAR	SOURCE OF FIGURES	CONFINE- MENTS	PROLAPSED CORDS	INCIDENCE PER CENT
1907 to 1922	Review of 8 reports, by Kurzrock ¹ Highest incidence in above Lowest incidence in above	260,437	2,408	0.92 Ave. 1.18 0.53
1932	Kurzrock's series ¹	16,942	100	0.59
1940	Mengert and Longwell ² Draa ³ Hillis ⁴ Providence Lying-in Hospital	9,546 5,035 9,581 36,773	63 18 25 155	0.66 0.35 0.26 0.42
	Composite figures for 1940	60,935	261	0.43 Ave.

The average incidence of 0.44 per cent for reports made in 1940 represents more than a 50 per cent reduction from that of 0.92 per cent computed from figures published between 1907 and 1922.

ETIOLOGY

Of the possible predisposing conditions analyzed in Table II, the abnormal pelvis and parity warrant brief discussion.

Whereas the standard textbooks^{5, 6} state that contraction is the principal bony anomaly predisposing to cord prolapse, one-half of the abnormal pelvis in this series were of the justo major type. The remaining half included 4 flat and 3 generally contracted pelvis, 2 android pelvis and 2 gynecoid with narrow forepelvis, 2 pelvis with prominent sacra and 1 with protruding promontory. The following case illustrates the role an abnormal pelvis can play in prolapse of the cord.

CASE 1.—(Unit No. 31,236.) A 40-year-old primigravida with a small male pelvis by clinical examination was to have a trial labor, with cesarean section held in

the attending staff. Table IV summarizes the individual methods employed. It may be stated that temporizing measures, especially postural treatment, prefaced the successful outcome of many cases with incompletely dilated cervixes; that efforts to open artificially the partially dilated cervix were, with the occasional exception of manual dilatation, uniformly unsuccessful; and that cases where immediate delivery through the completely dilated cervix was feasible were generally successful within the limits imposed by concomitant obstetric pathology.

Table V abstracts 51 successfully managed cases where cervical dilatation and station of the presenting part at the time of cord prolapse were

TABLE V. FIFTY-ONE SUCCESSFULLY MANAGED CASES OF CORD PROLAPSE WHERE CERVICAL DILATATION AND STATION AT THE TIME OF PROLAPSE WERE RECORDED

STATION	CERVIX	NO.	MANAGEMENT
High	2 cm.	1	Cesarean section
		1	Postural; cesarean section
	4 cm.	2	Postural; cesarean section
		1	Postural; artificial rupture of membranes; version and extraction
		1	Postural; artificial rupture of membranes; low forceps
	6 cm.	1	Postural; spontaneous delivery
		1	Manual dilatation of cervix; version and extraction
		1	Version and extraction
		1	Postural; low forceps
	8 cm.	2	Version and extraction
		1	Failed high forceps; version and extraction
		1	Manual dilatation of cervix; high forceps
	Compl.	4	Version and extraction
		1	Artificial rupture of membranes; version and extraction
		1	Postural; version and extraction
Mid	4 cm.	1	Artificial rupture of membranes; version and extraction
		1	Manual dilatation of cervix; breech extraction
		1	Postural; breech extraction
	6 cm.	1	Manual dilatation of cervix; breech extraction
		1	Manual rotation of head; midforceps
		1	Postural; breech extraction
	8 cm.	2	Manual rotation of head; midforceps
		1	Unsuccessful attempt at replacement; manual rotation of head; midforceps
		1	Failed midforceps; version and extraction
	Compl.	4	Version and extraction
		4	Midforceps
		1	Manual elevation of head; version and extraction
		1	Midforceps rotation and extraction
		1	Artificial rupture of membranes; manual rotation of head; midforceps
		1	Breech extraction
Low	6 cm.	2	Low forceps
	Compl.	3	Low forceps
		3	Breech extraction
		1	Spontaneous delivery

In the above cases, a time factor during which the cord was not fatally compressed frequently intervened between cord prolapse and ultimate delivery. Temporizing measures prolonged this time factor in many instances.

TABLE III. PRECIPITATING FACTORS IN 85 CASES OF CORD PROLAPSE

PRECIPITATING FACTOR	NO.	INCIDENCE PER CENT	FETAL MORTALITY	
			DIED	PER CENT
<i>Spontaneous</i>				
Rupture of membranes	27	17.4	18	66.7
Straining at stool	1	0.7	1	100.0
<i>Accidental</i>				
Rectal examination	1	0.7	1	100.0
Vaginal examination	3	1.9	1	33.3
Anesthesia (second stage gas-oxygen)	1	0.7	1	100.0
Artificial rupture of membranes	29	18.7	8	27.6
Corrected by deduction of two toxic cases with dead infants	27	17.4	6	22.2
Voorhees' bag	5	3.2	5	100.0
Dührssen's incisions	1	0.7	1	100.0
Manual rotation of head	10	6.5	6	60.0
Midforceps delivery	2	1.3	1	50.0
High forceps delivery	3	1.9	3	100.0
Internal podalic version	1	0.7	1	100.0
Internal cephalic version	1	0.7	0	0.0

epitated prolapse in 10 cases. Adherence to stricter qualifications for the performance of these procedures is seen as an important factor in the diminishing incidence of cord prolapse previously noted.

MANAGEMENT

The management of these cases was shared by 18 physicians attending private patients, and numerous residents under the supervision of

TABLE IV. INDIVIDUAL METHODS OF MANAGEMENT EMPLOYED IN 155 CASES OF CORD PROLAPSE

METHOD OF MANAGEMENT	NO.	FETAL MORTALITY	
		DIED	PER CENT
Spontaneous delivery	17	14	82.3
Postural treatment	20	5	25.0
Manual elevation of presenting part	1	0	0.0
Cord replacement			
Successful	3	1	33.3
Unsuccessful	12	6	50.0
Artificial rupture of membranes			
For forelying cord	5	1	20.0
For occult prolapse	3	0	0.0
Cervical tamponade	1	1	100.0
Dührssen's incisions	2	2	100.0
Voorhees' bag	4	4	100.0
Manual dilatation of cervix	14	9	64.3
Manual rotation of head	11	5	45.4
Forceps extraction			
Low	15	8	53.3
Mid	26	11	42.3
High	12	11	91.7
Breech extraction	31	13	41.9
Braxton Hicks' version	2	2	100.0
Version and extraction	52	25	48.1
Cesarean section	4	0	0.0
Craniotomy	2	2	100.0

More than one of the above procedures was employed in many cases. Note the mortality figures associated with operations directed at opening the cervix.

serious birth injury: 3 with brachial plexus paralyses, 2 with intracranial hemorrhage, 1 with facial paralysis, and 1 with a cephalematoma.

There were no maternal deaths, and 24, or 15.6 per cent, of the parturients experienced morbid puerperiums.

SUMMARY AND CONCLUSIONS

1. One hundred and fifty-five cases of cord prolapse occurred in 36,773 consecutive confinements with viable children at the Providence Lying-in Hospital, an incidence of 0.42 per cent. Comparison with other figures suggests that the incidence of cord prolapse is decreasing.

2. Of possible predisposing conditions the justo major pelvis assumed an importance equal to the contracted pelvis in this series. Multiparity played a minor, if any, causative role.

3. The commoner accidental causes of cord prolapse were artificial rupture of the membranes, the use of Voorhees' bag, and manual rotation of the head. It is felt that diminishing use of these procedures contributes to the diminishing incidence of cord prolapse.

4. Aside from pathologic conditions frequently associated with cord prolapse, the main obstacle to successful management was the partially dilated cervix. In these cases temporizing measures, especially postural treatment, were often successful in obviating pressure on the cord until delivery could be effected. Artificial methods of opening the cervix were for the most part unsuccessful.

5. Prolapse of the cord before the onset of labor, with both mother and fetus in good condition, presents a strong argument for cesarean section.

6. Infant mortality was 49.7 per cent, and 9 per cent of the living infants discharged from the hospital might be considered morbid. Maternal morbidity was 15.6 per cent; there were no maternal deaths.

I desire to express my gratitude to Dr. Bertram H. Buxton, Chief of Staff at the Providence Lying-in Hospital, for permission to review and present this series of cases.

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recorded. Scrutiny of these cases further emphasizes the fundamental importance of postural treatment. The author personally managed the following case which afforded opportunity to evaluate its efficacy.

CASE 2.—(Unit No. 35,396.) A multipara was admitted to the hospital in active labor with a hand, foot, and cord protruding through a cervix dilated 5 cm. The fetal heart tones became slow and slightly irregular with the patient in the horizontal position, and consistently returned to normal when she was placed in deep Trendelenburg. Except for three experimental periods when she was horizontal, the patient was maintained in Trendelenburg position for more than four hours, during which she experienced normal labor pains. Eventually the cord appeared at the introitus, and was becoming pulseless. Examination showed the cervix to be adequate, and a living child was delivered by version and extraction.

Four patients, each with cord prolapse occurring through a cervix less than one-half dilated, were successfully delivered by cesarean section. One abdominal delivery (Case 1) has already been described; the two following cases are of special interest:

CASE 3.—(Unit No. 15,328.) Prolapse of the cord occurred immediately after spontaneous rupture of the membranes in a 32-year-old multipara who was not in labor. Six hours later, still not in labor, she was admitted to the hospital with a loop of strongly pulsating cord hanging from the introitus. Cesarean section with removal of the prolapsed cord from below saved the infant's life.

CASE 4.—(Unit No. 35,203.) Artificial rupture of the membranes to induce labor precipitated prolapse of the cord in a 41-year-old toxic primigravida. She was placed in the knee-chest position while arrangements for operation were made, and in the Trendelenburg position while being prepared for operation. A 9-pound infant was delivered successfully by the abdominal route.

Since conservative treatment would almost certainly have condemned these infants, it is felt that cord prolapse in the absence of active labor, with both mother and fetus in good condition, constitutes a strong argument for cesarean section.

MORTALITY AND MORBIDITY

The mortality and morbidity statistics for this series appear in Table VI. Infant mortality lies within the generally accepted figures for cord prolapse. Subtraction of 22 cases where the fetus was considered dead on admission yields a 40.7 per cent fetal mortality for "treatable" cases. Infant morbidity assumes a substantial figure; of 78 living infants discharged from the hospital, 7 left with clinical evidence of more or less

TABLE VI. MORTALITY AND MORBIDITY STATISTICS

MORTALITY	NO.	PER CENT
Fetal deaths in 155 cases	77	49.7
Corrected for 1 neonatal death due to hemorrhagic disease of the newborn	76	49.0
Fetal deaths in 133 "treatable" cases	54	40.6
Maternal deaths	0	0.0
MORBIDITY		
Living infants discharged with birth injuries (total discharged living, 78)	7	9.0
Morbid puerperiums	24	15.6

soft, thick, and undilated. The fetus was estimated to be larger than average, and the fetal vertex was movable over the brim of the pelvis; the fetal heart was regular, 132 per minute.

Eleven hours after admission strong uterine contractions occurred regularly at five-minute intervals. Vaginal examination at this time revealed the uterine cervix dilated to admit two fingers and still thick. The vertex was still above the brim of the pelvis and no forewater was palpated.

At the end of twenty-four hours of labor, the cervix was found dilated to admit three and one-half fingers, and the vertex was fixed in the pelvic brim. Twenty-eight hours after the onset of labor, the patient experienced during the second stage of labor unusually severe labor pains, for the relief of which gas-oxygen was administered with each uterine contraction. The vertex crowned in the transverse position where its further progress was arrested. At this point, meconium was noticed coming from the vagina and the nurse reported that the fetal heartbeat, audible two minutes before, no longer could be heard. Ether was added to the gas-oxygen mixture to induce complete anesthesia. After rotating the head on the perineum, delivery of the fetus was accomplished easily with the aid of forceps. The baby was stillborn and weighed 11 pounds 8 ounces.

As the head was being delivered with forceps and while the patient was still under the influence of the anesthetic, the patient's respirations became irregular, shallow, and slowed to less than eight per minute. The pulse of poor quality became momentarily imperceptible, and then quickened to 144 per minute. Twenty minutes after the continuous administration of pure oxygen, intermittent injections of coramine, adrenalin, and intravenous (50 per cent) glucose, there was an improvement in the pulse and respiratory rate; the blood pressure reading was 160 systolic and 100 diastolic; but her general condition remained poor.

During the first stage of labor and prior to the administration of gas-oxygen, the patient was given two combined doses of $\frac{1}{8}$ gr. of morphine sulphate and $\frac{1}{200}$ gr. of scopolamine; and three doses of $\frac{1}{8}$ gr. of morphine sulphate, the last of these one and one-quarter hours before delivery.

The total duration of labor was twenty-eight hours and nine minutes, the first stage lasting twenty-seven hours and forty minutes, the second stage, twenty-three minutes, and the third stage, six minutes.

Approximately one hour following delivery of the fetus, there occurred muscular twitchings of the face, first involving the left and later both sides, extreme restlessness and unintelligible jabbering sounds. The eyes remained open and staring, the pupils were dilated, and the lower extremities were spastic.

Five hours after delivery the upper extremities became rigid. The patient tossed her head from side to side, cried out loudly, and thrashed around so much that restraint was necessary. The facial grimaces continued. She perspired a great deal and salivated considerably.

The patient cried out to painful stimuli about the face, but no movement of the arms or legs occurred. An examination of the cerebrospinal fluid twelve hours later showed 5 lymphocytes per c.mm. and a normal pressure.

The clinical picture forty-eight hours later was that of widespread decortication. All four extremities were paralyzed, a bilateral extensor toe sign being elicited. There was little movement about the mouth. The patient was unable to swallow and tube feeding was instituted. The optic fundi were normal. The patient cried out, was extremely irrational, and was incontinent.

The blood pressure rose to 190 systolic and 120 diastolic.

At the end of the first week, there occurred spasms of hyperpronation and adduction of the arms, with extension of both legs and conjugate deviation of the eyes in either direction. No attention was paid to her surroundings. The patient seemed completely devoid of intellect and to be purely vegetating.

At the end of the first month the patient answered questions, swallowed fluids, but generally remained out of contact with her environment, and was continuously incontinent. The lower extremities remained paralyzed, there was a fair amount of movement in the right arm and a trace of movement in the left arm. The muscle tone was increased throughout.

ANOXIA FOLLOWING NITROUS OXIDE ANESTHESIA FOR LABOR*

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COMPLICATIONS following nitrous oxide anesthesia have been known since this gas was first introduced as an anesthetic into surgery almost one hundred years ago. That death may occur during the administration of this anesthesia for minor procedures such as extraction of a tooth, is common knowledge. However, the occurrence of delayed deaths, the development of pathologic personalities, and other varied clinical pictures of organic brain disease caused by the use of nitrous oxide anesthesia have been reported only in the past few years.^{1, 2, 4, 5, 8-10} The anoxemia accompanying nitrous oxide anesthesia, either alone or combined with the effects of certain preoperative medication, has been shown to produce asphyxia of the brain cells or cerebral anoxia with its resulting necrosis of brain tissue.

Our interest in the potential danger of damage to the central nervous system caused by nitrous oxide was aroused by a recent experience in which a patient developed serious signs of diffuse brain damage when this anesthetic was used in the last stages of labor. To those who practice obstetrics, a field in which nitrous oxide anesthesia is so commonly employed, a discussion and survey of the literature is worthy of emphasis, especially since all the pertinent literature on maternal anoxia has been published in surgical, medical, or neuropsychiatric bulletins, and none was encountered in obstetric journals.†

Caine,⁵ in 1923, was the first to publish the records of 4 patients who manifested severe delayed cerebral changes, but it remained for Courville,¹ in 1936, to establish clearly the pathogenesis of cerebral anoxia following nitrous oxide anesthesia. Since his original excellent monograph, to which he has made valuable additions, there have been an increasing number of cases reported. To these we wish to add the following example of post-anesthetic encephalopathy with delayed death.

CASE REPORT

A. C., colored female, aged 31 years, para iv, gravida v, was admitted to the Obstetrical Ward Service of The Brooklyn Hospital June 30, 1940, with ruptured fetal membranes and irregular uterine pains. There was a normal prenatal course. The blood Wassermann test was negative and the blood pressure, urinalysis, and gain in weight were all within normal limits.

The previous deliveries were all uneventful, except for the third baby, which died at birth from an unknown cause. At The Brooklyn Hospital five and one-half years ago during the second stage of delivery of the fourth and last baby, gas oxygen anesthesia was administered without ill effects.

On examination, the patient showed no evidence of toxemia and was in good health, with normal heart and lungs. By rectal examination the uterine cervix was

*Presented at a meeting of the Brooklyn Gynecological Society, December 6, 1940.

†Careful study has been given to the problem of anoxia in the newborn infant by Eastman, Clifford, and others in contributions published in this JOURNAL and elsewhere, while the subject of mental deficiency in later life has been taken up by Schreiber, of Detroit (Proc. Am. A. Ment. Deficiency 63: 95, 1939).

There are four types of asphyxia or anoxia described, anoxic, anemic, stagnant, and histotoxic.^{4, 12} It is believed that a combination of all or several of these types results in serious complications.

The first type, anoxic anoxia, results from reduced arterial oxygen and depression of the respiratory center. In addition anything which will interfere with the respiratory mechanism such as disease of the lungs, or their accessory components, by diminishing the amount of oxygen inspired, will add to the danger of anoxia.

The second type, anemic anoxia, is due to a lack of, or inactivation of, hemoglobin, decreasing its capacity to take up oxygen. The third type, stagnant anoxia, results from retardation of the circulation which interferes with the transportation of oxygen.

The last type, histotoxic anoxia, is caused by drugging of the tissue cells so that they cannot utilize the available oxygen.

The following case reported by McClure and others⁴ illustrates all the above types of anoxia with fatality.

A white, unmarried female, with bilateral pulmonary tuberculosis and secondary anemia, was treated by pneumothorax. The last pneumothorax was performed July 14, 1938, when 375 c.c. of air was introduced into the left pleural space. Adenoidec-tomy was performed July 15, 1938, with 1½ gr. of nembutal, ¼ gr. of morphine sulphate, and 1/200 gr. of atropine as preoperative medication, and nitrous oxide-oxygen anesthesia. The anesthesia lasted only twenty minutes, but obvious cyanosis persisted throughout. The patient's condition was satisfactory when she was returned to her room an hour later, but she was still unconscious and cyanotic. One hour later respirations became labored and soon stopped. *Anatomic Diagnosis:* Asphyxia, blood uncoagulable; fibrocasseous tuberculosis; bilateral, chronic salpingitis. In this case the pneumothorax twenty-four hours previously and the nitrous oxide would account for anoxic anoxia; the secondary anemia for anemic anoxia; the surgical procedure for the low blood pressure and stagnant anoxia; and the pre-operative medication, nembutal and morphine for histotoxic anoxia.

Preoperative medication, principally morphine and the barbiturate derivatives, is capable of producing anoxia if used in moderate to large doses.⁴ Thus, the preoperative use of a barbiturate medication in large doses has been considered responsible for the only case of encephalopathy from cyclopropane in the literature.³ This is quite significant since cyclopropane has been heralded as an excellent anesthetic because of the high percentage of oxygen (77 per cent or more) reaching the patient during its administration.⁴ The barbiturates and morphine are respiratory and circulatory depressants, and, therefore, can add to the anoxic anoxia of anesthesia those of the histotoxic and stagnant types. In fact barbiturates alone if used in large doses can produce cerebral necrosis in both human beings and experimental animals.⁴ For this reason it would seem wise to use only the short-acting barbiturates in smaller doses as a preoperative medication. Many of the narcotics and anesthetics commonly used are capable of producing anoxia in some degree, although not enough to cause serious consequences. Should transitory failure of respiration and circulatory depression supervene, then asphyxia of the cortical cells takes place.¹

Other factors which may be responsible for anoxia have been traced to faulty gas machines, impurities of the gas, alcoholism on the part of the patient, or to the unskilled anesthetist.^{1, 4}

During the remainder of her stay in The Brooklyn Hospital, the mental and physical status remained unchanged. There was no fever except for a brief period caused by uterine infection. The blood pressure, normal on admission, remained consistently high, ranging around 190 to 210 systolic and 120 to 140 diastolic.

The patient was transferred to the Kings County Hospital where her condition gradually became worse until death occurred on Oct. 19, 1940, three and one-half months after the anoxic episode. A post-mortem examination was performed by the medical examiner. Grossly scattered minute areas of necrosis were found in the gray and white matter of the cortex and the gray matter of the base of the brain.

Brain.—Externally, the brain showed very little, but was very pale. No particular lesion was noted. The brain had already been cut horizontally in one section. In the fresh state, scattered discoloration of the gray matter of the cortex was seen. The surface was considerably shriveled. Fresh sections in the horizontal plane showed the following:

Widely disseminated, apparently degenerative lesions, involving the gray matter of the cortex with a striking tendency to involve the deepest layers of the cortex in laminar fashion. The most severe changes were in the occipital and parietooccipital regions where actual necrosis was observed and where the cortex was more extensively involved.

Elsewhere the lesions were granular and translucent. The area striata was grossly intact for the most part. On the right side there appeared to be a few similar lesions.

The section was through the superior part of the caudate which showed a few scattered grayish translucent spots of a similar type. The basal ganglia were less severely affected than the cortex. There were a few scattered grayish translucent areas (1 to 2 mm. in diameter) in ganglia. Most areas of the cortex seemed to be involved, at least in part, but not all areas.

One block through the parietooccipital region involving area of necrosis.

Other sections of the hemisphere revealed the same pathology.

The dentate nucleus (left) also has a granular appearance.

Brain stem showed no significant change. Olives were normal.

DISCUSSION

Nitrous oxide is thought to be the safest anesthetic for short operations. It is pleasant to take, causes no irritation, produces little excitement, and is supposedly free from aftereffect. Anesthesia from nitrous oxide is produced largely by exclusion of oxygen and partly by a direct narcotic action of the gas on the brain cells. Hence, the depth of anesthesia depends more upon the reduction of oxygen than upon the increased concentration of nitrous oxide.^{1, 6, 7}

The respiratory disturbances, convulsive features, and cyanosis produced by undiluted nitrous oxide are purely asphyxial or are associated with a state of anoxia, and, in practice, this state of asphyxia is prevented from reaching serious proportions by the addition of oxygen.⁷ However, to obtain successful surgical anesthesia it is necessary to administer 80 per cent to 95 per cent concentration of nitrous oxide,⁴ since anesthesia with this gas cannot be produced unless it is accompanied by some anoxemia. In the presence of ample oxygen where anoxemia could play no part, Brown, Easson and others⁶ were unable to produce anesthesia in experimental animals. McClure and his co-workers⁴ state that "Nitrous oxide-oxygen anesthesia of complete grade requires the reduction of the oxygen in the inspired mixture below maintenance levels (about 6 per cent), therefore, pure nitrous oxide anesthesia predicates anoxic anoxia." This is a dangerous small factor of safety when it is recognized that high concentrations of nitrous oxide are capable of producing brain damage.

2. The dangers of nitrous oxide anesthesia as a cause of delayed deaths, pathologic personalities, and other varied clinical pictures of organic brain disease are emphasized to those who practice obstetrics.

3. The case history of a patient who developed severe brain damage following nitrous oxide anesthesia for labor and died three and one-half months later is reported.

4. The pathologic observations reported in the literature are summarized.

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DISCUSSION

DR. HAROLD R. MERWARTH.—Attention has been called to this condition only since 1923 and especially since 1936, when the work of Courville of California appeared.

The clinical picture in the case presented was essentially that of widespread decortication. The patient suffered both visual and auditory hallucinations, was virtually completely paralyzed, had to be tube-fed, and was continuously incontinent.

An interesting point which was not emphasized in the history was the fact that at no time did the blood pressure drop below 190 or 200 points. This was probably explained by the autopsy findings in the left kidney which was completely eliminated by infarcts. There was also damage to the right kidney and other changes in the lungs. The brain was disappointing on gross examination and on cutting required careful inspection to find the damage done. This was essentially limited to the gray matter of the cortex and lenticular nucleus, involving chiefly the innermost cells of the gray matter of the frontal, occipital, and temporal lobes. There also was damage to the dentate nucleus of the cerebellum. The changes noted in this specimen are not found characteristically in carbon monoxide poisoning, but would account for the mental symptoms in the case.

Had the patient survived, the resulting damage would have been such that she would always have manifested symptoms of a chronic deterioration of the brain in the form of a paralysis agitans or tremors of the athetoid type.

Himwich has shown that the highest rate of metabolism occurs in the gray cells of the cortex. In this case the patient was deprived of oxygen and consequent damage might be expected to occur in that location. It also is a fact that barbiturates slow up cellular metabolism in the brain, and consequently whenever a patient receives nitrous oxide there should always be a careful inquiry of how much barbiturates she has received.

DR. ALEXANDER H. ROSENTHAL.—The Committee on Analysis of Maternal Deaths in Brooklyn, during the years 1937, 1938, and 1939, assigned the primary cause of death in 13 patients to the anesthetic employed, in a series of 387 consecutive maternal deaths from all causes. The record compares unfavorably with the report of maternal mortality in New York City for the years 1930 to 1933 in which anesthesia was considered the direct cause of death in 20 cases out of a total of 2,041 deaths. The frequency of death from anesthesia in Brooklyn was thus more than three times as high.

A review of the 13 deaths showed that five were in patients delivered by cesarean section, four by forceps, three spontaneously, while one patient was undelivered.

The clinical picture caused by nitrous oxide asphyxia is bizarre, although certain features are fairly constant. In some of the cases reported, the patients died in respiratory failure while still on the table; others who recovered from a temporary cardiorespiratory failure developed delayed symptoms soon after returning to their rooms, and still others whose behavior during the anesthetic was apparently satisfactory, likewise, developed symptoms as late as hours or days after operation. Cardiorespiratory failure on the table, so commonly reported in itself, adds to the anoxia produced by the anesthetic and preoperative medication. Cyanosis during the anesthesia may or may not be present, and is not necessarily an index of the degree of anoxemia. In several of Courville's fatal cases, cyanosis was notably absent.

The patient may never react from the anesthetic, but remain comatose. Muscular twitchings varying from mild restlessness to severe convulsions, decortication phenomena or rigidity, and hyperthermia are all indicative of cerebral damage.⁹ Death may follow after a variable interval. Those who survive are mentally confused and manifest athetoid movements and visual disturbances. Undoubtedly, many minor transient cases recover unrecognized.

These symptoms are better understood in the light of the observations at autopsy which vary with the period of survival, and resemble closely the changes noted in patients dying from carbon monoxide poisoning and acute alcoholism. Courville^{1, 2} and McClure's group⁴ have recorded their necropsy findings in detail.

In patients dying within twenty-four hours, the gross examination revealed engorgement of the pial and cerebral blood vessels. The lungs were voluminous and of increased density as a result of edema and congestion. Microscopically, the essential changes in the brain were pericellular and perivascular edema, shrinkage of the pyramidal cells of the cortex and other ganglion cells; and cuff hemorrhages especially in the basal nuclei. In the lungs, hemorrhagic infiltration (hemorrhagic pneumonia) was present. Small hemorrhages were occasionally seen in the cortex of the adrenal glands and kidneys.

When death followed after an interval of two days or more, areas of hemorrhage and necrosis were observed in addition to all the above changes. While in some instances the necrosis was limited to focal areas in the cortex, in others, the entire lobes were involved. The individual cells were seen in stages of liquefaction, lipiodol degeneration, and calcification. The lungs either showed resolution of the hemorrhagic pneumonia of the acute phase, or had progressed to frank consolidation of lobular distribution. Hemorrhage and tubular degeneration were present in the kidneys.

CONCLUSIONS

1. Anoxemia accompanying nitrous oxide anesthesia, either alone or combined with the effects of certain preoperative medication, has been shown to produce asphyxia of the brain cells or cerebral anoxia with its resulting necrosis of brain tissue.

JELLY CONTRACEPTIVES*

A THREE-YEAR INVESTIGATION

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ASSISTED BY RITA NIELSEN, R.N.

(From the Michael Reese Hospital and Northwestern University Medical School)

SOME ten years ago, one of us (Stein) concluded a three-year study using jelly alone for contraception in a series of 146 fertile women. These patients, observed from six months to two years, using a 2 per cent lactic acid jelly with chinosol, were afforded a high degree of protection. In fact, during the course of the active clinic, no pregnancies were discovered and only after the clinic was disbanded and patients spread over the five regular gynecologic clinics of Mandel Clinic, did a number of pregnancies occur. Records of some of these women who are still registered at Mandel Clinic show that they have used jelly continuously and effectively up to the present time.

In the interim, we have followed this method of contraception to some extent in our private practice with a degree of success sufficient to warrant another inquiry as to its efficacy, using modern and improved preparations which are now commercially available. We have felt that there is a definite need for a simple, safe and inexpensive single method of birth control, one which will prove to be acceptable to both husband and wife, and be within easy reach when needed. Such a method must also be one not likely to lessen natural desires and responses; it must be effective as a contraceptive and at the same time harmless to the patient. Consequently, when requested by the National Committee on Maternal Health to investigate "jelly alone" again, we reorganized a special Birth Control Clinic at the Mandel Clinic of the Michael Reese Hospital.

It was decided that this clinic should accept *medical referrals only*, no voluntary requests for birth control being granted. Patients were referred from the gynecologic, postnatal, psychiatric, medical (especially cardiac and tuberculosis), and other departments of Mandel Clinic. Careful records were kept and a history of previous pregnancy and labor, abortions, and previous birth control experience were particularly noted. Reasons for acceptance or refusal of patients for jelly contraception were recorded, and the kind of jelly and applicator issued was stated (Figs. 1 and 2). Upon follow-up visits, questions were asked and answers recorded as to whether instructions were followed; discontinuance of the method or omission; whether or not the jelly was satisfactory to husband and wife; objections to the method; whether pregnancy occurred while the method was in use. In the event of the latter, further inquiry was made into reasons for the same.

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Three patients received only spinal anesthesia. In one of the deaths, anoxia, of a type Dr. Turino has described tonight, may have occurred. In 5 patients death was due to vomiting and aspiration, 2 proved at autopsy by the presence of food particles in the tracheobronchial tree. In two cases general anesthesia was used in the presence of toxemia.

The dangers in the use of anesthesia in obstetrics should be well known, and certain facts self-evident.

1. The administration of a general anesthetic should be reduced to a minimum. In spontaneous deliveries, the perineal stage of labor and the episiotomy with its repair can be more safely done under local anesthesia, which especially is indicated in toxemia, cardiac disease, tuberculosis, and upper respiratory infections.

2. The stomach should be free of food before the induction of general anesthesia.

3. The risk of general anesthesia is increased in the presence of toxemia.

4. Spinal anesthesia should not be used by the occasional obstetric operator. It carries particular dangers for the pregnant woman.

DR. FREDERICK C. WILCOX, JR.—George Savage of Great Britain, in 1887, reported a case like this one in the *British Medical Journal*. His patient was an alcoholic, a young woman, who became frankly demented after nitrous oxide anesthesia, and evidently she did not recover. Courville, of Los Angeles, and Batten, of Battle Creek, in a recent article in *Anesthesiology* reported 10 cases, 5 of which had previously been reported. The end-results in all these cases ranged from complete recovery down through impairment of memory and emotional instability, to death.

Four of these reported cases had definite secondary anemia, so that with the anoxia produced by the nitrous oxide there undoubtedly was some anoxia due to anemia. It is of interest to note that 6 of the patients were obstetric and gynecologic cases. The explanation for so many of these cases in obstetrics possibly may be that obstetric patients at term, as a rule, have a higher basal metabolic rate than usual, sometimes being 20 per cent above normal, and need a greater percentage of oxygen than under ordinary circumstances.

Nitrous oxide, as has been stated, depends partially upon anoxia for its anesthetic action. It has hazards, except under most ideal conditions, and I should like to state the conditions which I think are ideal for its use: “(1) The basal metabolic rate should be normal. (2) The blood count and hemoglobin should be approximately normal. (3) There should be no history of chronic alcoholism. (4) Adequate pre-medication should be given the patient. (5) The patient should be of the white race.”

DR. CHARLES A. GORDON.—It is absolutely impossible to get anesthesia with nitrous oxide in any concentration that does not approach 100 per cent. Otherwise we get analgesia but not anesthesia. The anesthetist, when he or she finds that the operator is dissatisfied, is likely to crowd the percentage of gas so that it approaches very undesirable levels.

From what we know about nitrous oxide, and the autopsy findings in this case, I believe that undue concentration was used. No one should use it unless he pays attention to the anesthetist so as to make sure that the concentration is as the operator thinks it should be; otherwise it is dangerous. Nitrous oxide has a great many advantages and when combined with local anesthesia and proper infiltration, it is safe and satisfactory.

RESULTS

Altogether, 310 patients were registered in the special Birth Control Clinic. Two-thirds reported that they had previously used various and often multiple contraceptive methods more or less unsuccessfully. Only 79 women reported that they had previously used no means of contraception, and it is more than likely that a number of these had practiced coitus interruptus, the one single method most frequently employed by those who admitted previous birth control. The next in order of frequency were the postcoital douche and the condom, reported in about equal numbers. The douche proved to be the most disastrous, yielding a high percentage of undesired pregnancies, practically paralleling those who used no previous birth control. The condom gave the highest degree of pre-clinic protection. The use of a diaphragm and jelly combination was reported by a relatively small group (22 women) with failures in more than half the cases. However, many of these failures might be attributed to the fact that instruction in the use of the diaphragm was inadequate, some having purchased the materials in drug stores or obtained them from physicians untrained in birth control procedures. A small group used jellies for varying periods up to eight years. A few of these were holdovers from our former clinic. Fully one-fourth of the group reported having tried a variety of methods, single and combined, but generally with unsatisfactory results.

To evaluate the effectiveness of jelly alone as a contraceptive agent, the method of Pearl as modified by Stix and Notestein was adopted. Pregnancy rates were computed for patients before using the clinic prescription and compared with those obtained after using the jelly method. *The pregnancy rate is expressed in the following equation: The number of pregnancies divided by the exposures in years to the risk of pregnancy, multiplied by 100.*

The effectiveness of the method is expressed as percentage reduction in fertility. A summary of the effectiveness of jelly alone in our three-year study gave a total reduction in fertility of 87.1 per cent.

Failures were considered from the standpoint of: (1) failure of the jelly-alone method as instructed; (2) failure to use the method, or irregular use; (3) failures after discontinuing the method, including planned pregnancies; (4) failures in women who used other methods than the one prescribed.

1. There were 20 patients in the entire series who presumably became pregnant while using the jelly alone as instructed. These must be construed as true failures, and in terms of percentage, constitute 8.6 per cent of patients who remained in the clinic from three months to three years.

2. There were 18 women who admitted inconstant use of jelly and omission of the preparation at the time of conception. These obviously cannot be termed as jelly failures.

3. Three women discontinued the method in order to become pregnant (planned pregnancies).

4. Two pregnancies occurred in women who were relying upon condom protection instead of the prescribed jelly. In addition, a miscellaneous group included one who was judged incompetent to follow even the simple instructions of the jelly technique.

There was a total of 47 women who became pregnant, including the planned pregnancies, in the entire group. Seventeen of these delivered at term and 8 were pregnant at the termination of the clinic. The wastage may be expressed by 2 stillbirths, 9 spontaneous and 5 induced abortions. In addition, there were 6 whose terminations were unknown.

SUMMARY

1. It has been shown by Stix that birth control measures are not equally effective in reducing the risk of pregnancy in the various social

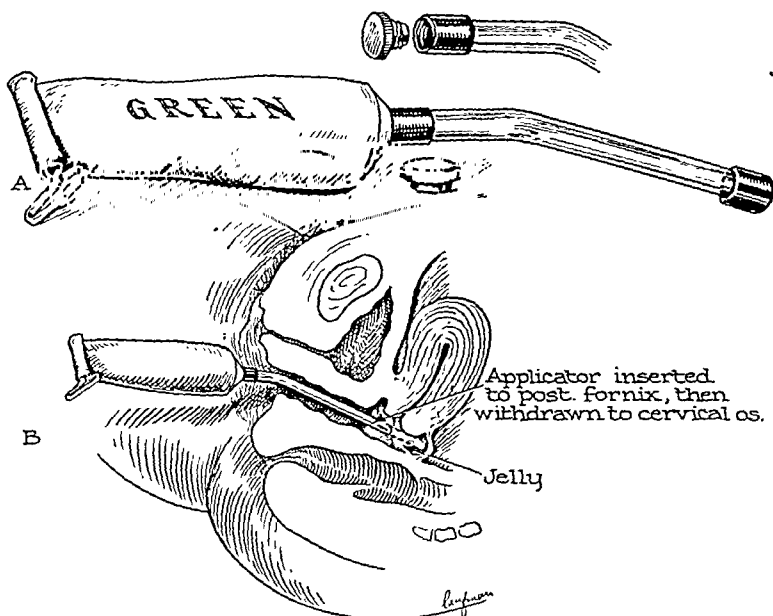


Fig. 1.—"Green" jelly. Key dose control. Attached nozzle. *Formula*: Lactic acid, 2.0 per cent; oxyquinoline sulphate, 0.05 per cent; durekol base (made of especially blended carbohydrate gums), pH 2.9.

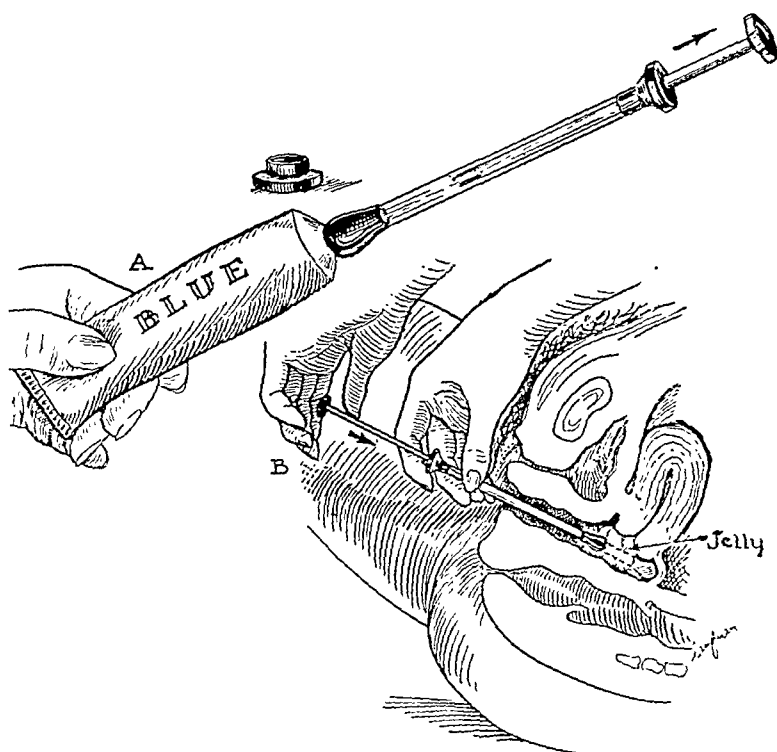


Fig. 2.—"Blue" jelly. Measured dose applicator. *Formula*: Glycerin, 10.0 per cent; vegetable gum, 5.0 per cent; boric acid, 3.0 per cent; ricinoleic acid, 0.75 per cent; propyl ester of para-hydroxy-benzoic acid, 0.05 per cent; oxyquinoline sulphate, 0.025 per cent; perfume, 0.05 per cent; water to 100.0 per cent. The pH is 4.5.

utilizing the technique with complete success for long periods of time. Of this group, a few were so well satisfied with the method that they refused sterilization which had previously been proposed.

Jelly alone should be included in the list of approved contraceptive techniques.

DISCUSSION

DR. FRED L. ADAIR.—We have had no experience whatever in our clinic with the use of jelly alone. We have used various other methods which seemed to be approved and most generally used in other clinics. Our situation is somewhat different from Dr. Stein's and other so-called birth control clinics, because we run our contraceptive clinic simply as a part of the Maternity Guidance Clinic. It is open only to patients who come to the clinic for other purposes. Second, most of the patients who receive contraceptive advice are those who require it for medical complications. We have had no experience with methods that are not considered reliable, as we do not feel justified in experimenting with patients to whom pregnancy would be a hazard.

The great difficulty with all contraceptives from a sociologic point of view is that the methods do not reach the people who need them most. It is all right to find a method which is harmless, which is used by a little over one-third of the people who apply to the clinic, and which is effective when properly used by patients in 87 per cent, which still leaves 13 per cent of failures. There are many people who do not continue to use it even though they seek advice at the clinic. Also, there is a great mass of people who from the standpoint of environment, heredity, and other conditions should have this sort of advice but who never get into a birth control clinic. So from the standpoint of sociologic problems involved, it has always seemed to me that we are not reaching the patients who need to be reached the most. However, that is no reason for not employing these methods as indicated in individual cases. Two years ago we presented before this Society a procedure which is relatively harmless, much more effective, and one in which the patient does not need to use her intelligence, the so-called post-partum sterilization. This procedure was not received too kindly in this Society, but we have continued to employ it nevertheless. From other clinics we have received favorable reports. One of our former residents now located in Puerto Rico, where the control of conception is badly needed, has had a considerable series of cases in which post-partum sterilization has proved both satisfactory and safe. In those patients who should never become pregnant again, I would call attention to this post-partum sterilization which is safe and does not menace the patient in the properly selected cases when properly performed.

DR. H. O. MARYAN.—About three years ago I helped develop a contraceptive jelly, and made a study of the patients along clinical and laboratory lines. I should like to report some observations made in 30 cases.

We first took into consideration the psychic reaction; that is, the presence or absence of local irritation. I do not know of any article in the literature that takes up this phase. I think that this is very important because of the toxicity of the various contraceptive jellies. Another phase we took into consideration was the healing value in irritations of the vagina and cervix, and also the spermaticidal value.

One of the most usual complaints of the patients was that the jelly was "messy" and that it would run out during the night. However, many husbands were not aware of the fact that their wives were using jelly. Women like it because it is cleaner, and also because it gives a better vaginal odor, as well as the fact that it aids in healing areas where biopsies were taken. We made biopsies from the vagina in five cases. The pharmaceutical house also made cervical and vaginal biopsies on monkeys before the jelly was used in women. We found there was no cervical or vaginal irritation after the patient had used the jelly for several months. The patients were instructed to use the jelly every night. These specimens were checked

classes. She concluded that the condom is only 65 per cent effective in relief recipients in comparison with 88 per cent effectiveness in white-collar workers. The clientele represented in our study was drawn essentially from families on relief.

2. Of the 310 patients who registered in our Birth Control Clinic at Mandel Clinic, 231 remained active for a period ranging from three months to three years. They made a total of 816 clinic visits. Most of the patients who accepted the method and cooperated with us were contented with it.

3. An analysis of preclinic experience revealed that two-thirds of the patients had previously used various birth control methods, both single and combined, with unsatisfactory results.

4. A total of 47 pregnancies occurred in the active clinic group, but when these histories were analyzed, only 20 could be charged against the jelly-alone method.

5. The results of this study confirm our opinion regarding the value of the jelly-alone method which was based upon our previous experience with this method a decade ago.

6. The effectiveness of jelly alone as a contraceptive is shown by the 87.1 per cent reduction in fertility. This compares most favorably with the results of the diaphragm and jelly method which Stix has shown was only 76 per cent effective in relief recipients, a clientele similar to ours.

7. Acceptability of the method is proved by the fact that while 37 per cent of the total group, or 50 per cent of the group active in the clinic for some time, used the method, a very small number had any real objection to or complaint against the method. Because of the low acceptability of any single method of birth control, multiple techniques should be available in birth control clinics.

8. In our opinion, *it is the jelly and not the diaphragm that is the potent factor in the diaphragm and jelly technique of contraception.*

CONCLUSIONS

Early in this discussion we have defined what we consider the basic requirements for a simple and safe contraceptive, namely: that it must prove acceptable to both husband and wife; it must always be within easy reach; it should not lessen natural desires and responses; it must be effective and at the same time harmless. The jelly-alone method in our experience measures up to these standards.

In conclusion, we believe that clinics should not limit their procedure to a single method, but should adopt a more flexible policy of utilizing the various accredited techniques, fitting the contraceptive to the needs of the individual patients. Whenever the patient is dissatisfied with the method prescribed, a different one should be substituted, thereby not only suiting the contraceptive to the patient, but also increasing her confidence in the method. So far as the jelly-alone method is concerned, many patients who had been judged as below average in intelligence and who were supposedly unable to follow directions, proved capable of

fourteenth days, respectively, of an artificial cycle. Fig. 5 shows a mild degree of cystic glandular hyperplasia produced after the third attempt to produce withdrawal bleeding in Patient M. M. The total dose of diethylstilbestrol used for this cycle was 70 mg. These histologic findings are in agreement with the report of Wenner and Joël,⁴ that more than 60 mg. of diethylstilbestrol may produce hyperplasia. Forty-two milligrams have been an optimum dose of diethylstilbestrol for the production of normal endometrial proliferation in fourteen days. Estrogenic hormone was absent from the urine of the 4 patients listed in Table I when treatment was

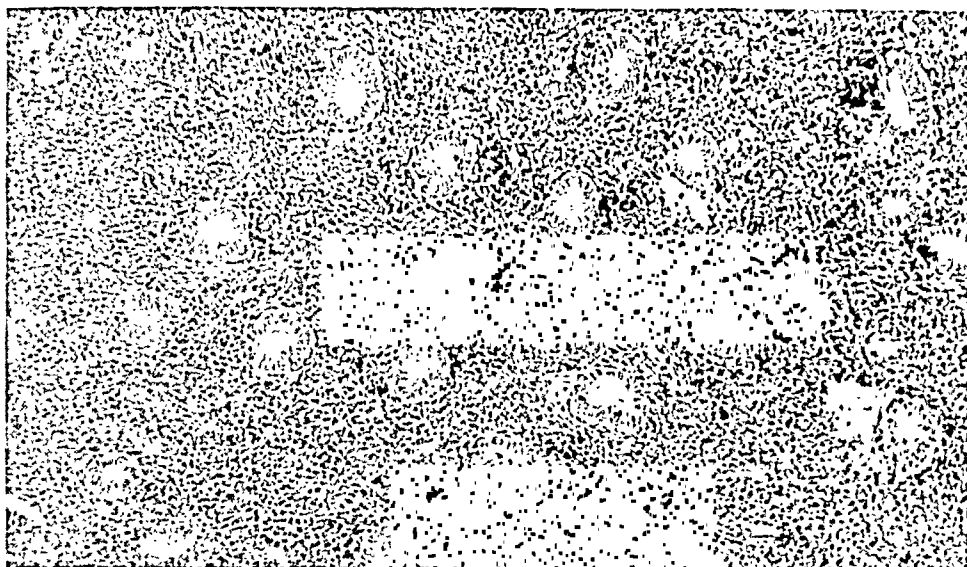


Fig. 3.—Photomicrograph of inactive endometrium obtained at the beginning of an artificially produced threshold cycle in Patient M. P. ($\times 120$.)



Fig. 4.—Photomicrograph of normal proliferative endometrium obtained on the fourteenth day of an artificially produced threshold cycle in Patient M. P. A total dose of 42 mg. diethylstilbestrol was given. Bleeding occurred from this endometrium eleven days later ($\times 120$).

ovulatory cycle in which progestin takes part has also been simulated and produced artificially (Zuckerman⁷); this particular issue is not, however, relevant to the clinical experiment under discussion.

Fluctuation of Uterine Threshold in the Monkey.—The fluctuating uterine threshold has been demonstrated by Zuckerman⁵ in an ovariectomized monkey which was injected daily for 365 days with the same amount of estrone (10 gamma per day). In spite of the repeated injections, eight separate phases of bleeding occurred during the experiment but at intervals varying from five to seven weeks. In view of the fact that uterine bleeding will not occur in spayed monkeys under continuous injection with an amount of hormone that is well above threshold value (100 gamma per day), the successive phases of bleeding observed in this monkey must be interpreted as reflections of successive falls in the degree of estrogenic stimulation experienced by the animal or successive rises of the uterine threshold. Since the monkey was being continuously injected with the same amount of hormone daily, it follows that rhythmical changes of a kind that decreased the effectivity of the hormone occurred within the animal itself. The possibility that the adrenals and the pituitary are in some way concerned is being investigated.

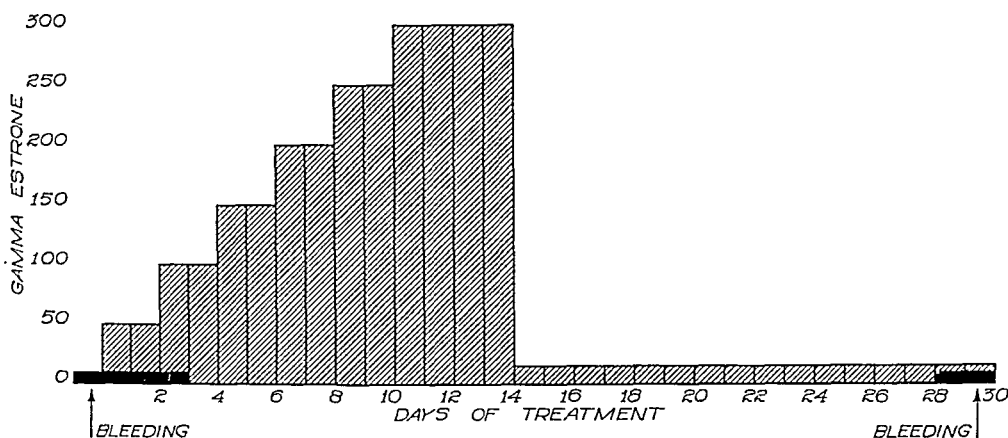


Fig. 2.—Threshold cycle in monkey produced with estrone. Length of cycle prolonged from 22 to 28 days with daily subthreshold dose of estrone from fifteenth day forward. (Zuckerman, 1937.)

ARTIFICIAL CYCLES IN THE HUMAN BEING

I have used diethylstilbestrol in the human being to induce cyclical estrogen withdrawal bleeding. Wenner and Joël⁴ and Wenner³ report that a minimum total dose of 25 mg. of diethylstilbestrol orally is required to produce what appears to be normal endometrial growth, while a dose of 60 mg. or more may produce endometrial hyperplasia. The availability of 1 and 5 mg. tablets of diethylstilbestrol resulted in the adoption of the following plan for the production of an artificial estrogenic cycle in the human subject: 1 mg. per day for seven days followed by 5 mg. per day for seven days. Thus one course of therapy would amount to a total dose of 42 mg.

The treatment of 4 patients with primary amenorrhea in this manner was usually followed by uterine bleeding after a latent interval of five or six days (Table I). Prolongation of the latent interval was effected in 3 artificial cycles by giving a subthreshold dose of 0.1 or 0.3 mg. of diethylstilbestrol daily from the fifteenth day onward. The pH of the vaginal mucosa before and during each cycle of therapy is shown in the last two columns of Table I. Figs. 3 and 4 show the histologic structure of the endometrium obtained by biopsy from Patient M. P. on the first and

TABLE I*

PT.	DIAGNOSIS OF AMENORRHEA	AGE	NO. OF CYCLE	TREATMENT (DIETHYLSTILBESTROL)	LENGTH OF CYCLE DAYS	LATENT INTERVAL BET. CESSATION OF TREATMENT AND BLEEDING	VAGINAL pH	
							BEFORE TREATMENT	DURING TREATMENT
M. P.	Primary (genital hypoplasia)	16	1	42 mg. in 14 days	20	6 days	6.0	4.0 4.0
			2	7 mg. in 7 days	-	No bleeding	4.8	- -
			3	42 mg. in 14 days	20	6 days	4.8	4.0 4.0
			4	42 mg. in 14 days	25	3 days	5.2	4.0 4.0
			5	0.3 mg./day 15th-22nd day 42 mg. in 14 days	21	Bleeding 22nd day during treatment	-	4.0 -
G. A.	Primary (pituitary infantilism)	24	1	42 mg. in 14 days	-	No bleeding	6.0	4.4 4.0
			2	42 mg. in 14 days	19	5 days	4.8	4.0 4.0
			3	42 mg. in 14 days	19	5 days	4.4	- -
			4	19 mg. in 19 days	24	5 days	-	4.0 -
D. S.	Primary (genital hypoplasia)	18	1	7 mg. in 7 days	-	No bleeding	7.6	- -
			2	7 mg. in 7 days	-	No bleeding	6.8	5.2 -
			3	52 mg. in 14 days	21	Bleeding 22nd day during treatment	6.0	4.0 -
			4	0.3 mg./day 15th-22nd day	-	-	-	-
M. M.	Primary (genital hypoplasia)	20	1	42 mg. in 14 days	-	No bleeding	6.0	4.0 -
			2	42 mg. in 14 days	-	No bleeding	5.6	4.0 -
			3	70 mg. in 14 days	19	5 days	5.6	4.0 -

*Data pertaining to threshold cycles produced artificially in the human being with diethylstilbestrol.

TABLE II*

PT.	DIAGNOSIS OF AMENORRHEA	AGE	NO. OF CYCLE	TREATMENT (DIETHYLSTILBESTROL)	LENGTH OF CYCLE DAYS	LATENT INTERVAL BET. CESSATION OF TREATMENT AND BLEEDING	VAGINAL pH	
							BEFORE TREATMENT	DURING TREATMENT
I. O.	Secondary (natural menopause 5 years)	58	1	38 mg. in 21 days	24	4 days	5.6	4.8 -
			2	21 mg. in 21 days	-	No bleeding	5.6	5.2 -
			3	5 mg. in 1 day	6	5 days	5.6	4.4 -
J. D.	Secondary (natural menopause 30 years)	81	1	14 mg. in 14 days	19	5 days	7.2	- -
			2	14 mg. in 14 days	20	6 days	-	6.8 -
			3	49 mg. in 14 days	19	5 days	-	4.8 -
			4	42 mg. in 21 days	27	6 days	-	- -
J. N.	Secondary (natural menopause 6 years)	52	1	21 mg. in 21 days	-	No bleeding	7.6	4.4 5.2
			2	2.8 mg. in 14 days	-	No bleeding	5.2	4.0 -
			3	42 mg. in 14 days	20	6 days	5.0	4.0 4.0
			4	23 mg. in 23 days	28	5 days	5.6	4.0 5.0
			5	36 mg. in 18 days	30	Bleeding 31st day during treatment	-	4.8 4.8
V. N.	Secondary (natural menopause 5 years)	44	1	21 mg. in 21 days	26	5 days	5.0	4.4 -

*Data pertaining to threshold cycles produced artificially in the human being with diethylstilbestrol.

started. To date there has been no spontaneous occurrence of menstruation following substitution therapy, other than the immediate withdrawal bleeding.

Variations in the administration of diethylstilbestrol were tried in 4 post-menopausal patients whose pelvic organs were intact (Table II). It is noted (1) that the lengths of the artificial estrogenic cycles varied with the duration of therapy when the daily dose was 1 or more mg.; (2) that when the daily dose was decreased to 0.1 to 0.3 mg. bleeding occurred during therapy although the latent interval between the fall of daily dose and the onset of bleeding was prolonged; (3) that the latent interval between complete cessation of therapy (when the daily dose was 1 mg. or more) and the onset of bleeding was consistently five to six days; and (4) that the pH of the vagina was lowered in every instance following estrogen therapy.

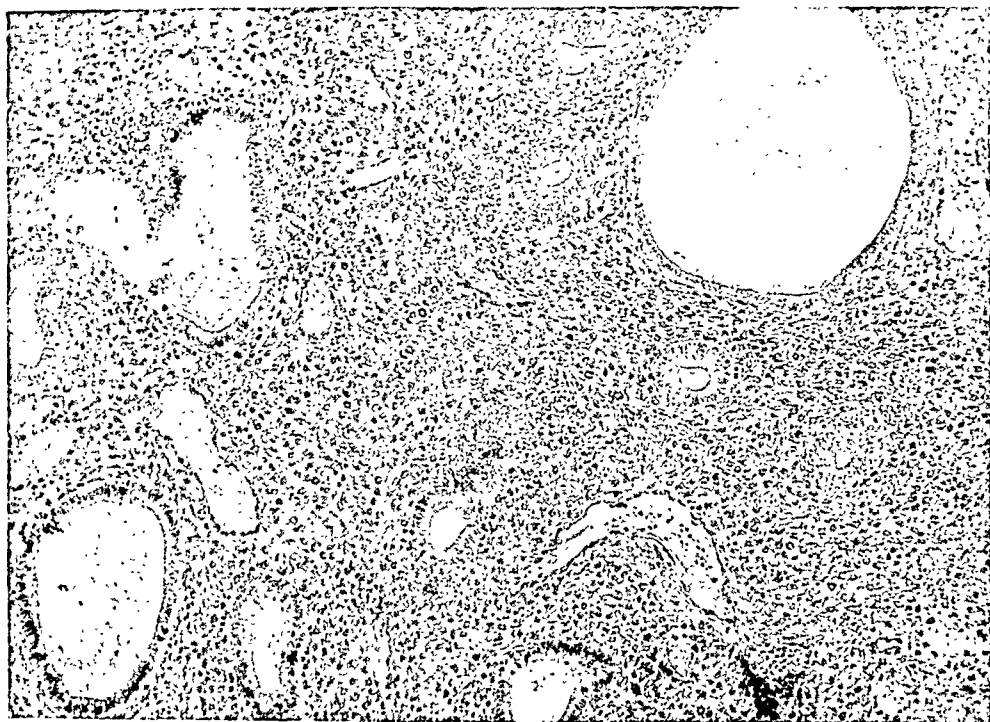


Fig. 5.—Photomicrograph of cystic endometrium obtained from Patient M. M., after a total oral dose of 70 mg. diethylstilbestrol in fourteen days. ($\times 120$.)

DISCUSSION

The purposes for which the clinical experiments reported in this paper were intended are: (1) To ascertain the oral therapeutic dose of diethylstilbestrol necessary for the production of normal endometrial proliferation and estrogen-withdrawal bleeding in women without ovarian function. (2) To estimate the amount of diethylstilbestrol administered by mouth over a period of fourteen days which would produce abnormally hyperplastic endometrium. (3) To produce, by cyclical estrogen therapy, artificial menstrual cycles in women according to Zuckerman's interpretation of "threshold cycle" as it pertains to the monkey. (4) To demonstrate the presence or absence in the human being of a *fluctuating* uterine threshold to diethylstilbestrol.

It is admitted, for the present, at least, that probably there is no particular reason for inducing uterine bleeding by substitutional therapy. However, definite growth of the uterus and development of

THE PRESENCE OF EXCESSIVE AMOUNTS OF GONADOTROPIC PRINCIPLE IN THE URINE OF PATIENTS WITH THYROID DISEASE

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AMONG myxedematous women, Zondek¹ only infrequently found an increased urinary output of the gonadotropic principle. Among five women with severe exophthalmic goiter, he found only one who had an increased output of the gonadotropic principle. Our interest in the relationship of thyroid dysfunction to the function of gonadotropic principle was stimulated by observations made in the case which follows:

REPORT OF CASE

An unmarried woman, 35 years of age, came to the Mayo Clinic in April, 1937, and was dismissed in August, 1938. This patient was concerned about a goiter, the presence of which first had been noted ten years earlier and which had been gradually growing to its present size. She also was concerned about gradually increasing nervousness, palpitation, weakness, and loss of weight, which had been progressively worse for two to three years. Since the menarche at twelve years of age, the menses seldom appeared oftener than once a year. The right eye had been noticeably more prominent than the left for an unknown length of time. These difficulties had never been incapacitating.

On admission, the patient weighed 131 pounds (59.4 kg.). The blood pressure, measured in millimeters of mercury, was 110 systolic and 64 diastolic; the pulse rate was 73 beats per minute. The thyroid was diffusely enlarged; each lobe measured about 1 by 2 inches (2.5 by 5 cm.). There was a moderate degree of lag and retraction of the right eyelid. The left eye appeared normal. Pelvic examination gave negative results. The basal metabolic rate was normal.

Thyroidectomy was considered but never urged. Since the patient volunteered a decided unwillingness to consider such a procedure, medical treatment was instituted. Lugol's solution, 10 drops three times a day, was given. Because of the amenorrhea, one of us (D. G. D.) had the urine assayed for the gonadotropic principle. Sixty-six rat units of gonadotropic principle and 20 R.U. of estrin were demonstrated per liter of urine (Fig. 1, *a* and *b*). The patient was under observation for about sixteen months. In this time the basal metabolic rate gradually fell to -17 per cent and the weight on dismissal had increased to 151 pounds (68.5 kg.). At dismissal, the gonadotropic principle was not demonstrable in the urine. The thyroid may have become a little larger and was definitely softer in consistency than on admission. There was no striking improvement in the exophthalmos as measured by the exophthalmometer, but the edema and retraction of the lids had become less noticeable. The patient's general health was subjectively improved. During all this period of observation her symptoms never interfered with continuous employment as a domestic.

This study has been made in an attempt to demonstrate what influence, if any, thyroid disease has on the urinary output of gonadotropic prin-

other secondary sexual characteristics were effected by cyclical estrogen therapy along with periodic uterine bleeding. There is considerable experimental evidence that prolonged uninterrupted estrogen treatment produces undesirable results that are not produced by cyclical therapy (Palmer¹).

The importance of cyclical estrogen therapy has been revealed by an investigation of the case history of Patient M.P. (Table I). For seven and one-half months this patient received thrice-weekly injections and oral doses of one estrogen or another without periods of observation for withdrawal bleeding. Efforts had been directed toward the development of mammary tissue for cosmetic reasons and the establishment of the menarche. Withdrawal bleeding of two days' duration occurred finally six days after the cessation of the long uninterrupted course of estrogen therapy. Following the first attempt at cyclical therapy, withdrawal bleeding occurred six days after a threshold cycle of diethylstilbestrol, and endured four days.

SUMMARY

1. Zuckerman's experimental data on the production of artificial menstrual cycles and a fluctuating uterine threshold to estrone in the monkey are reviewed.

2. Artificial menstrual cycles (diethylstilbestrol withdrawal bleeding) were induced by cyclical diethylstilbestrol therapy in 4 patients with primary amenorrhea and in 4 postmenopausal women.

3. Forty-two milligrams were found to be an optimum oral dose of diethylstilbestrol which in fourteen days would produce a normal degree of endometrial proliferation and would be followed by uterine bleeding.

4. Seventy milligrams of diethylstilbestrol by mouth in fourteen days produced a slight degree of cystic glandular hyperplasia of the endometrium.

5. The consistency of the latent interval that precedes withdrawal bleeding in the group of primary and postmenopausal amenorrheic patients, regardless of variation in dosage and manner of administration, leads one to believe that a *fluctuating* uterine threshold to estrogen may not be a factor with which to be concerned as it will be shown to be in patients with uterine bleeding (Palmer²), and as it is known to be in the ovariectomized monkey.

The diethylstilbestrol used in this investigation was supplied by the Eli Lilly and E. R. Squibb Companies.

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(A second contribution to this subject will appear in the June issue of the JOURNAL.)

from 10 men. Three of these men were hospitalized patients who had received surgical treatment for an injured tendon of hand, tuberculosis of spine, and inguinal hernia, respectively. The others were physicians who were in good health.

The Method of Assay.—Twenty-four-hour specimens of urine were collected. Four hundred cubic centimeters of the specimen were concentrated for gonadotropic principle according to Frank's acetone method. This method makes use of the fact that gonadotropic principle is precipitated out of the urine on addition of acetone. The hormone-containing precipitate is extracted. The extract is adjusted to an optimal pH and a volume of 8 c.c. so that the gonadotropic principle in the extract is 50 times more concentrated than in urine. This material is assayed on immature rats as has been described.² These investigators accepted the presence of stimulation of the ovarian follicles viewed in serial sections as evidence of the presence of the gonadotropic principle in the urine. The yield of gonadotropic principle is expressed in terms of rat units per liter of urine. In nearly every case an effort was made to demonstrate yields of 25, 40, and 66 R.U. per liter of urine.

THE DATA

The Excretion of Gonadotropic Principle by Normal Individuals.—None of the thirteen young, healthy, normally menstruating women observed by Osterberg and one of us (Drips) excreted more than 20 R.U. per liter. In our studies of the urine excreted by normal men we found 20 R.U. of gonadotropic hormone per liter excreted on only one occasion by one person. A second specimen yielded 10 R.U. per liter and a third specimen from this subject failed to reveal any gonadotropic principle. All assays of urine from the other normal men revealed less than 20 R.U. of gonadotropic principle or none at all. On the basis of these data, it would seem that normal individuals may excrete as much as 20 R.U. or less of gonadotropic principle per liter of urine. This variation in excretion compares favorably with the findings of other investigators. There are not enough data at hand to tell us how often normal individuals excrete more than 20 R.U. per liter of urine.

The Excretion of Gonadotropic Principle in the Urine of Patients With Thyroid Disease.—A summary of our observations is given in Table I. The patients were grouped according to type of thyroid disease and sex. The yield of gonadotropic principle was assigned in accordance with an arbitrary quantitative division or grouping (Table I). A yield of 25 R.U. or more is probably definitely excessive. Therefore this division was used. In the first group are all yields of 24 R.U. per liter or less; in the second group, all yields of 25 to 40 R.U. per liter; and in the third group, all yields of 40 R.U. or more. Assay of more than one specimen of urine was obtained in some cases, but only the report of the first assay has been utilized for the data in Table I. Sections of ovaries from rats used in assay of gonadotropic principle in two cases are presented in Figs. 2, *a* and *b* and 3, *a* and *b*.

ciple. Assays of 101 specimens of urine from 63 patients suffering from various thyroid diseases were made for the gonadotropic factor.

PROCEDURE

The Selection of Patients.—Since we lacked precedent, the urinary output of gonadotropic principle of all patients with thyroid disease was studied at first. A total of 63 patients were examined. Because excessive amounts of the gonadotropic principle are excreted during the menopause, we decided to exclude from this study the data obtained on all women forty years of age or more. There were 10 such patients. We

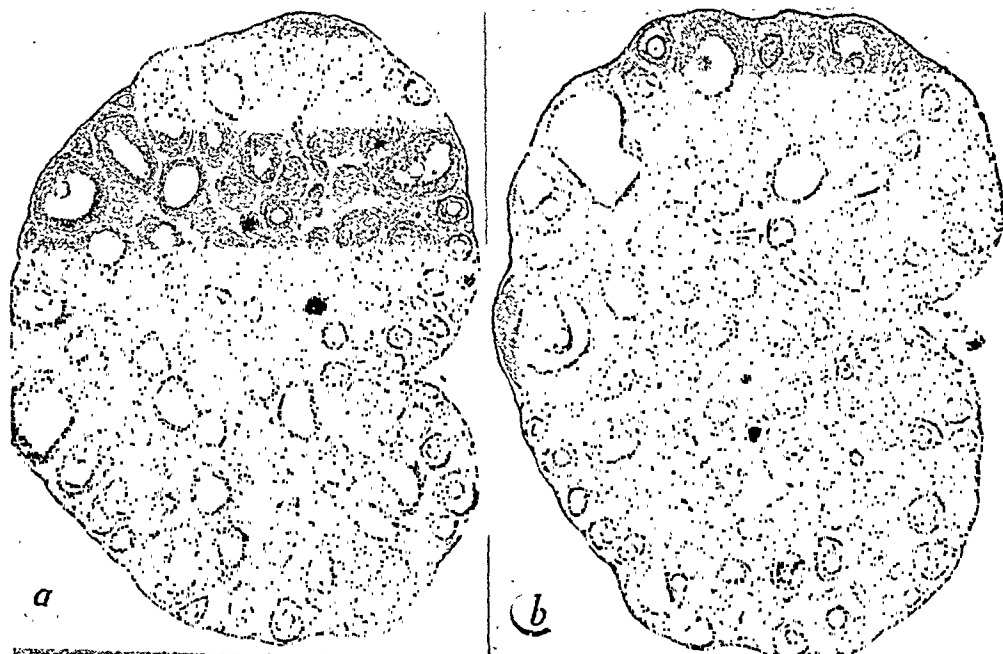


Fig. 1.—Sections of ovaries from rats used for assay of gonadotropic principle: *a*, control; *b*, from litter mate of rat used for control, after injection of urine from a woman aged 35 years, with exophthalmic goiter; assay indicates presence of 66 R.U. of gonadotropic principle per liter.

are reporting, therefore, the results obtained from examination of 53 patients: 22 men and 31 women. These patients had a variety of thyroid diseases or dysfunctions. The ages of the males ranged from 19 to 60 years; of the females from 8 to 39 years.

The Selection of Controls.—There are numerous accounts in the literature of quantitative determinations for the gonadotropic principle in the urine of normal individuals.

Comparison of our data with that from these sources proved difficult, partly because the methods of assay were not always identical with ours and partly because the series of cases was sometimes rather small. Osterberg and one of us (Drips²), who described the method of assay employed in this study, examined the urine of 13 healthy, normally menstruating young women. Their data have been utilized as our control study for the excretion of gonadotropic principle by women. To supplement this series we analyzed 17 twenty-four-hour specimens of urine

COMMENT

This study was undertaken to determine whether thyroid disease was a factor in the excretion of the gonadotropic principle and particularly in the excretion of increased amounts. In analyzing the case histories an attempt was made to select such data as might have some actual or theoretical bearing on the output of gonadotropic principle. Thus, we made note not only of the patient's age, sex, and type of thyroid disease, which are indicated in Table I, but also the duration of the thyroid disease, the height of the basal metabolic rate, the catamenia and the history of using iodine (excluding the possible use of iodized salt).

TABLE I. GONADOTROPIC PRINCIPLE IN URINE IN 53 CASES OF THYROID DISEASE

DISEASE	TOTAL CASES	RAT UNITS PER LITER OF URINE		
		24 OR LESS	25 TO 40	40 OR MORE
<i>Males</i>				
Exophthalmic goiter*	16	12	3	1
Exophthalmic goiter with adenoma*	4	3		1
Exophthalmic goiter suspected	1	1		
Myxedema	1		1	
<i>Females</i>				
Exophthalmic goiter*	16	11		5
Adenomatous goiter with hyperthyroidism*	5	3		2
Adenomatous goiter without hyperthyroidism*	2	2		
Exophthalmic goiter suspected	5	2	1	2
Myxedema	2		1	1
Artificial hyperthyroidism	1	1		
Male	22	16	4	2
Female	31	19	2	10
Total	53	35	6	12

*Diagnosis proved at operation.

Within the limitations of this study no definite correlations were found. Certain evidence, however, is clear. The type of thyroid disease, such as exophthalmic goiter, adenomatous goiter, or myxedema, does not determine that the urine will contain large amounts of the gonadotropic principle. Similarly, large amounts are present in the urine of patients of both sexes with thyroid disease and in the urine of patients who have low as well as those who have elevated basal metabolic rates. In the presence of thyroid disease urine voided at any time in the menstrual cycle may contain large amounts and women with normal as well as irregular menstrual periods are capable of excreting increased amounts. It is impossible to say what effect age has on this phenomenon. It is notable, however, that one girl, eight years of age, who had exophthalmic goiter, excreted excessive amounts. All the men who excreted 25 R.U. or more of gonadotropic principle per liter of urine were less than fifty years of age. Among women use of iodine might be a possible factor in suppressing the excretion of excessive amounts of gonadotropic prin-



Fig. 2.—Ovaries from rats: *a*, control; *b*, from litter mate of rat used for control after injection of urine from woman aged 29 years, with exophthalmic goiter; assay indicates 66 R.U. of gonadotropic principle per liter of urine.

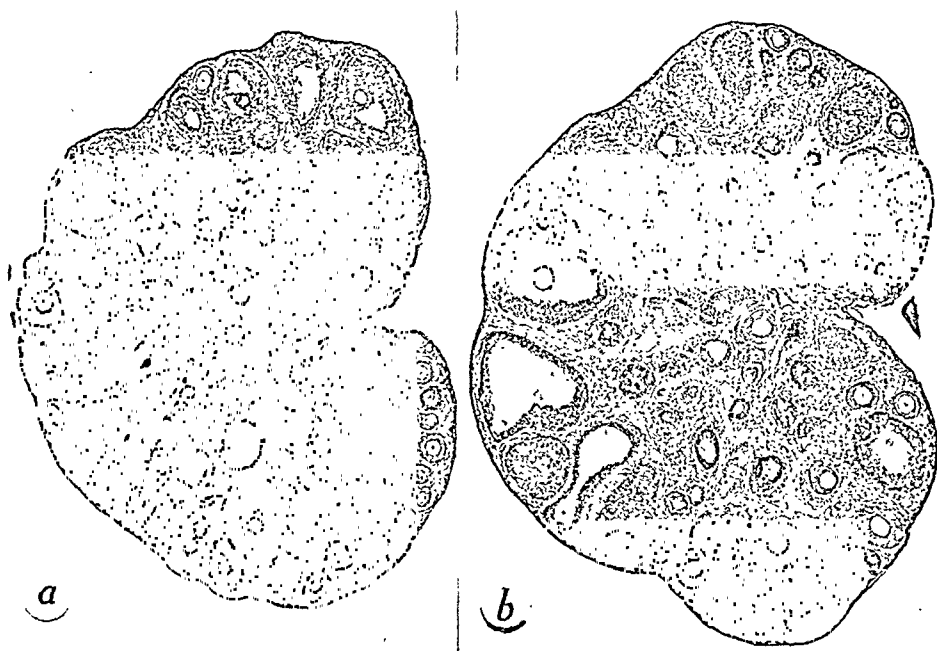


Fig. 3.—Sections of ovaries from rats used for assay of gonadotropic hormone: *a*, control; *b*, from litter mate of rat used for control after injection of urine from a man, aged 38 years, with exophthalmic goiter; assay indicates 66 R.U. of gonadotropic principle per liter of urine.

in this substance which apparently possesses progestational, estrogenic, and androgenic activity³ (see discussion), we have used pregneninolone clinically during the past twelve months. Experimental data obtained with rabbits and rats appear in another report (in press).

The 28 female patients comprising this study were seen both in private practice and in the Evanston Hospital Out-Patient department. Oral pregneninolone was employed in the treatment of unexplained or "functional" endocrine disorders. All known local or systemic factors, such as genital pathology or thyroid deficiency, which might have been of etiologic significance were ruled out. Usually other types of endocrine therapy had been tried first without the desired effect. A summary of clinical data is included in tabular form (Table I).

TABLE I. SUMMARY OF CLINICAL DATA

CASES	COMPLAINT	DOSE	RESULTS
6	Menorrhagia	200-1,140 mg. in 14 premenstrual days	No beneficial effects
2	Premenstrual tension	210-270 mg. in 14 premenst. days	Excellent in one Variable in one
6	Dysmenorrhea	210-560 mg. in 14 premenst. days	Excellent in one Variable in four Worse (?) in one
4	Secondary amenorrhea	230-300 mg. in 14 days or less	Bleeding after each trial of medication
3	Threatened abortion	40 mg. daily for 2 days, 3, and 12 days	2 aborted. 1 delivered at term, after 5 weeks of spotting in the third and fourth months
2	Sterility	40 mg. daily for 14 premenst. days. 20 mg. (same)	Secretory endometrium Early secretory endometrium No pregnancies
2	Menopausal symptoms	30 mg. daily for 12 days	Beneficial (?) in one No effect in one
3	Nausea of pregnancy	20-40 mg. daily	Dubious effect in all

It has not been possible always to predict the effect, if any, of pregneninolone from month to month, even in the same patient. This was especially true in the treatment of dysmenorrhea—a complaint in which psychic and environmental factors are notoriously difficult to evaluate. Occasionally the results of therapy were striking, but in most cases the substance was of very dubious value.

Of particular interest were 4 cases of secondary amenorrhea. Since the history and response to therapy of each were similar, one summary will suffice:

M. M., first seen in November, 1939, at 23 years of age, had had but 6 episodes of vaginal bleeding since the menarche at 16. About every thirty days she would have a feeling of pelvic congestion and fatigue, but usually had no menstrual flow. Her past history was essentially negative, and for the past twelve months her basal metabolic rate had been maintained at 0 to +12 per cent with 2 gr. of desiccated thyroid daily, with no change in her menstrual history. Previous to

ciple. We have observed that the excretion of gonadotropic principle may vary considerably in amount from day to day in the same individual.

On the basis of this study it is not possible to explain why some patients with thyroid disease excrete excessive amounts of gonadotropic principle and others do not.

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CLINICAL EXPERIENCE WITH PREGNENINOLONE*

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IN 1938 Inhoffen and Hohlweg,^{1a} by adding the ethynil radical to estradiol, produced the synthetic estrogen ethynil estradiol. This substance was remarkable in that it was very effective when given by mouth, but it had too many undesirable side-actions for clinical use. These same workers added the ethynil radical to testosterone, and presented a new synthetic product called variously Δ 4-pregnene-in, 17-ol, 3-one, ethynil testosterone, anhydro-oxy-progesterone, or pregneninolone.¹ In this paper it will be called pregneninolone. It was unique in having a marked corpus luteumlike effect upon the endometrium of rabbits when given orally. Even pure progesterone, generally considered to be the corpus luteum hormone, has no appreciable action when given orally.¹ Yet it was shown that the minimal effective dose of pregneninolone in immature female rabbits (first "primed" with estrogen) was only 4 mg., while 60 mg. of progesterone orally had no effect. Clauberg and Üstün⁸ and Salmon, Walter, and Geist⁶ have shown that in postmenopausal patients a secretory endometrium ensues when estrogenic therapy is followed by 300 to 500 mg. of pregneninolone orally. Hamblen and co-workers¹¹ have reported the production of a secretory type of endometrium in irregularly menstruating women with pregneninolone. Zondek and Rozin⁹ were able to induce bleeding in a normally menstruating female in midcycle with 280 mg. of this substance given orally, an effect which also followed the injection of 50 mg. of progesterone.^{9, 10} They also induced bleeding in secondary amenorrhea with 300 mg. of pregneninolone by mouth, but not after only 220 mg.⁹ Courrier and Jost² have maintained pregnancy in rabbits castrated during pregnancy with oral pregneninolone.

Because of the possibility of obviating costly and time-consuming injections of progesterone, and also because of the academic interest

*The generous supply of pregneninolone was furnished by the Ciba Pharmaceutical Products, Inc.

tions are identical throughout with those of progesterone. One usually considers the sex hormones, all of which are chemically related sterols, to be divided into 3 distinct groups: estrogenic, androgenic, and progestational. The estrogens provoke estrus changes in the female genital tract, or those changes occurring during the follicular phase of ovarian activity, such as a proliferative type of endometrium and cornification of the vagina. Androgenic substances stimulate male sexual structures, for example, the prostate, seminal vesicles, penis, and cock's comb. Progestational changes are found during the life of the corpus luteum, and include the secretory phase of the endometrium, decidua formation, mucification of the rat vagina, and allegedly, depression of uterine irritability. In general, these sex hormones exhibit a special predilection for specific reproductive structures. Possibly because the molecular structures of these sex-sterols are very similar, there is some overlapping of biologic effect, especially when large doses are used. To cite but two of many examples, large doses of progesterone produce definite androgenic effects,¹² while certain doses of androgens as well as estrogens will cause growth,¹³ edema and hyperemia¹⁴ of the rat uterus.

Emmens and Parkes³ first noted that pregnenolone not only had progestational activity, but also produced signs of estrogenic stimulation in the rat vagina, and evidence of androgenic stimulation in the cock's comb. Courrier and Jost² observed androgenic changes in the castrated rat and chick's comb with pregnenolone. One of us (E. S. B.) has also obtained these apparently conflicting effects in experimental animals, as well as additional evidence that pregnenolone and progesterone are not biologically identical.

It has been tempting to hypothesize that pregnenolone during the process of digestion and absorption is converted into the chemically very similar progesterone. Yet histologic studies of pregnenolone-treated animals are not completely similar to those observed under progesterone treatment. Furthermore, the physiologic responses of the uteri of rabbits treated *in vitro* with the 2 substances are quite different, i.e., progesterone-treated uteri do not react to relatively large amounts of oxytocins, such as pituitrin, while pregnenolone-treated uteri manifest a marked increase in uterine tone and magnitude of contraction when pituitrin is given. This observation alone should provoke much hesitation before employing in threatened abortion a substance acting differently from the frequently recommended progesterone.

The use of pregnenolone to produce bleeding in secondary amenorrhea probably amounts to more than crude empiricism. Since, in the 3 cases presented, there were no objective signs of estrogenic deficiency except amenorrhea, one must assume that enough estrogen was present to prevent other signs of estrogen-lack (such as vulvar, vaginal, uterine, or breast atrophy). It is known that small amounts of estrogen potentiate the action of progesterone upon sexual structures. It is, therefore, theoretically possible to produce a progestational endometrium with a substance such as pregnenolone which has some progestational properties and to obtain bleeding from this "prepared" endometrium.

thyroid therapy her basal metabolic rate had been -18 per cent and -21 per cent. Pelvic findings were not unusual. The cervix appeared and felt normal; the corpus uteri was anterior, small, but not infantile. The adnexa felt normal by bimanual palpation, though the right ovary had been reported fourteen months previously as "slightly enlarged" by another doctor. Her weight was consistently 155 to 160 pounds, height was 5 feet 9 inches, contours and hair distribution were of the feminine type, and her mental adjustment to her life was good. Her only complaints were that she "wanted to be like other girls," that she wanted a family after marriage, and that she "felt better after menstruating."

An endometrial biopsy at this time showed a thin "resting" type of endometrium. In January, 1940, she began to bleed on the thirteenth day of medication, after having taken a total of 270 mg. of pregnenolone by mouth. This flow lasted for five days. Likewise, in February, 1940, three days after 260 mg. in twelve days, she had a four-day flow. For the next three months, she received no medication, and had no bleeding. In June she had two days of vaginal bleeding, beginning on the twelfth day of therapy, after a total of 230 mg. of pregnenolone. Again in July, after 280 mg. of pregnenolone in ten days, she bled for three days. An endometrial biopsy on the first day of this bleeding was of an early secretory, or progesterational type. In August, bleeding occurred on the eleventh day of therapy, after 300 mg. of pregnenolone; the biopsy on the first day of flow was also of an early secretory phase of the endometrium.

TOXICITY

We were especially interested in the possible toxicity of this new substance. When the ethynil radical was added to estradiol, the oral effectiveness of this estrogen was greatly enhanced (16 times),¹ but there were many unpleasant side actions in the human being, chiefly referable to the gastrointestinal tract. There has been only one report to date of the toxic effects of pregnenolone; and the doses used, experimentally and clinically, were not large. Hamblen and co-workers¹¹ have given comparatively very large doses, as high as 2,280 mg. in fourteen days, and we have used up to 1,140 mg. in fourteen days without untoward effects. None of our patients voluntarily complained of any distress, and when questioned, offered no definite evidence of variation from previous states of health. One of us ingested 270 mg. of pregnenolone at one dose and experienced no symptoms. In 81 experimental animals which were being studied concomitantly, the livers, kidneys and adrenal glands were examined grossly and histologically. There were no pathologic changes in these pregnenolone-treated animals. By limiting their water supply to one containing a suspension of the pure crystals, two rats were induced to take the relatively tremendous doses of 655 and 730 mg. of pregnenolone in twelve and eighteen days, respectively. The first animal was killed at the cessation of treatment, and the other three weeks after medication was stopped. Neither showed gross or histologic evidence of damage to the above list of essential organs.

DISCUSSION

Pregnenolone has been given by the oral route to 28 female patients presenting complaints in which progesterone therapy is thought by many to be beneficial. That the results of this therapy have not been encouraging is admittedly due in part to the difficulty of treating disorders whose etiology is so largely a matter of conjecture. From experimental evidence one cannot conclude that pregnenolone's ac-

all near term. Each animal was prepared for experimentation after the method of cerebral anemia suggested by Swenson¹⁰ and used in a previous investigation published by Mitchell and Pankratz.¹¹ Under light ether anesthesia both common carotid arteries were quickly ligated and usually a heavy ligature was tied around the entire neck musculature, sparing the vagi and trachea. The trachea was cannulated and no further anesthetic was used. Animals were then strapped to a special aluminum board and the uterus exposed through a midline incision. This procedure usually took only about ten minutes.

A thread for recording was tied into the serosa of a suitable uterine segment, in an area not over the placenta and rather avascular. The entire lower half of the animal fastened to the animal board was then immersed in a large bath of mammalian Ringer's solution. This solution was kept at a constant temperature of from 37.5° to 38.5° C., and stirred mechanically. The uterine segment to which the thread was attached was free in the bath except for its anatomic anchorage. Care was taken to preserve the blood supply of uterine segments studied. Kymographic records were made by means of a heart lever attached directly to the thread.

Animals thus prepared were observed for three to seven hours, without difficulty. A control record of uterine activity was usually made for one hour or until a typical contraction record was obtained. During a previous series of experiments,¹¹ we had observed that the rabbit, the guinea pig, the cat, and the dog each had a definite uterine contraction pattern. Veterinary nembutal was administered on a weight basis, 0.1 c.c. (0.1 gr.) for each pound of animal weight. This dosage is recommended as a surgical dose. In all of our experiments two or three such doses were given at intervals varying from one to three hours. The nembutal was given either subcutaneously or intramuscularly. No difference was observed in the two methods, except that the latter was quicker. The effectiveness of the nembutal was checked by either pulling on the peritoneum or pinching a foot, and by the respiration which became slower but even and usually deeper.

RESULTS

The normal uterine movements in all animals consisted of frequent circular contractions, and slower but more powerful longitudinal contractions. These could be easily distinguished both by the eye and by the character of the kymograph record.

PREGNANT RABBITS

The uteri of these animals were all quite active, the ones nearest term being most active. In all the experiments it seemed that as soon as the drug began to take effect the uterus would manifest an even and typical contraction pattern. The tracings shown in Figs. 1 and 2 were taken of a rabbit twenty-six days pregnant. This animal was observed for seven hours and during that time received 0.2 gr. of pentobarbital sodium per pound. The uterus was active and the animal in good condition at the end of the experiment.

POST-PARTUM RABBITS

Three rabbits were studied within one day after delivery and found to be very active. Fig. 3 is a kymograph record obtained from a doe that had delivered the day before the experiment. She was observed for over five hours and received subcutaneously 0.2 gr. of nembutal per pound in two doses within one hour.

The uterine contraction of four rabbits in estrus was also studied. Such uteri are less active as was pointed out in a previous publication.¹¹ The administration of nembutal in doses of 0.1 to 0.2 gr. per pound animal weight showed no definite suppression of uterine motility.

GUINEA PIGS

Only 3 guinea pigs were used, but these were near term. The first dose of 0.1 gr. of nembutal per pound caused no change in uterine contractions (Fig. 4), and

SUMMARY AND CONCLUSIONS

1. Pregneninolone, a new synthetic product, when given orally produces a progestational type of endometrium.

2. It has no detectable toxic effects in laboratory animals or in the human being when given in the relatively large doses used in our studies.

3. In general, it has not been of clinical value. Its possible mode of action in producing bleeding in secondary amenorrheics has been discussed.

4. It cannot be considered to have effects identical with those of progesterone.

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OBSERVATIONS ON THE EFFECTS OF PENTOBARBITAL SODIUM (NEMBUTAL) ON THE INTACT UTERUS OF ANIMALS*

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THE prominent role occupied by the barbiturates for analgesia during labor is evident from the reports of Averett,¹ Clifford and Irving,² Galloway and Smith,³ Jones,⁴ Kane and Roth,⁵ King,⁶ and many others. Among the barbiturates used, pentobarbital sodium (nembutal) has no doubt been administered most extensively and successfully. Two outstanding experimental works are those of Adair and Pearl⁷ and Gruber.⁸ Recently Tatum⁹ has thoroughly reviewed the present status of the barbiturates. Since so much interest in nembutal is manifest, further experiments on intact uteri of some laboratory animals were considered worth while.

METHODS

The animals used in the experiments were for the most part rabbits, supplemented by guinea pigs, cats, and dogs. Twenty-five animals were used, most of them in the latter part of pregnancy. A few post-partum rabbit uteri were studied. The breeding dates of all the pregnant rabbits were known, and the other animals were

*The nembutal was kindly furnished by the Abbott Laboratories.

the fetuses remained active. But when a second similar dose was given an hour later, the fetuses first made kicking movements in utero, and then became inactive. A number of them died in utero, and at the end of the experiment it was found that the placentas were detached. The uterus continued to contract.

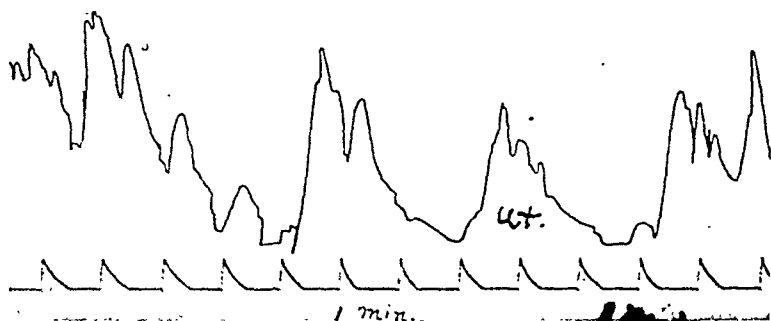


Fig. 4.—Tracing showing uterine contractions in the guinea pig near term. Record taken one and one-half hours after second dose of nembutal (each dose 0.1 gr. per pound).

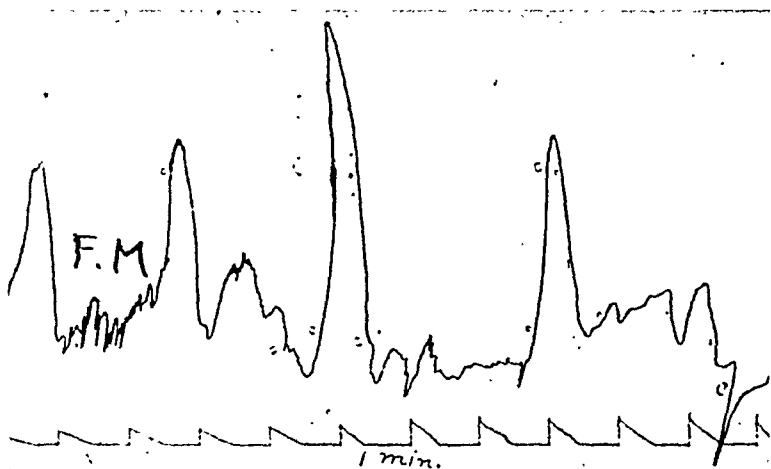


Fig. 5.—Tracing of uterine contractions in a cat near term. Record made three hours after the first injection and two hours after the second injection. *F. M.*, indicates fetal movements.

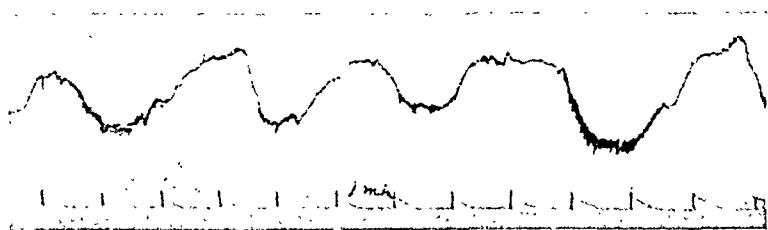


Fig. 6.—Tracing of uterine contractions in a dog near term. Record made two hours after the second injection of nembutal (0.1 gr. per pound, each dose). The small changes in the tracing are due to maternal respiration which is not depressed.

CATS

A small number of cats was used. Here again the first dose of 0.1 gr. of pentobarbital sodium per pound caused no change in uterine contractions or in the behavior of the fetuses (Fig. 5). A second similar dose within one hour caused the fetuses to kick in utero, the mother to breathe slower, but the uterus showed no

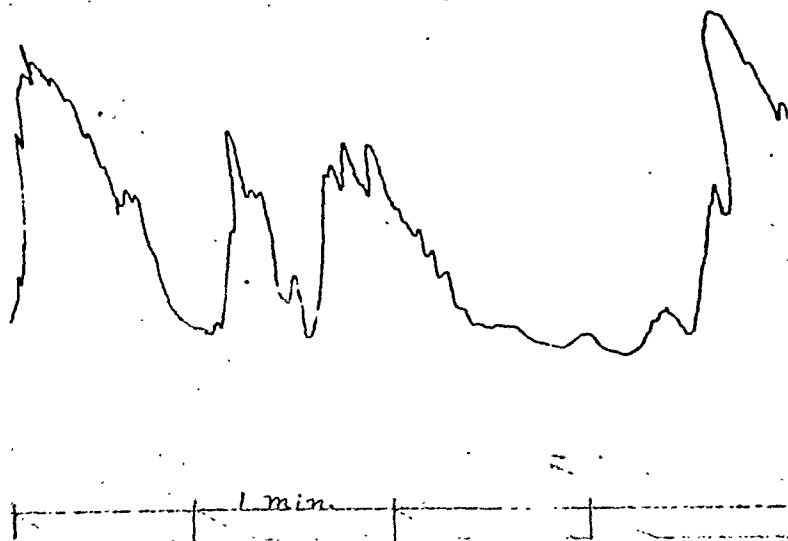


Fig. 1.—Tracing of uterine contraction in a rabbit twenty-six days pregnant. The record was made before any nembutal had been administered.

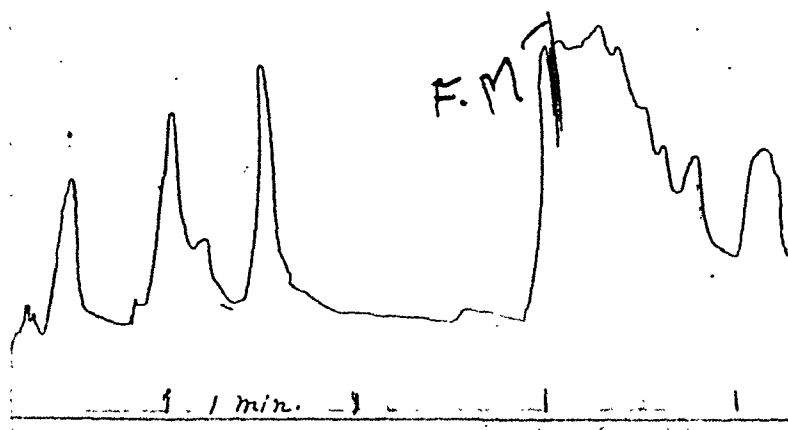


Fig. 2.—Tracing of uterine contractions in the same animal as shown in Fig. 1, but three hours later and soon after second dose of nembutal (0.1 gr. per pound). *F. M.*, indicates fetal movements in utero. Four fetuses were removed before this graph was made.

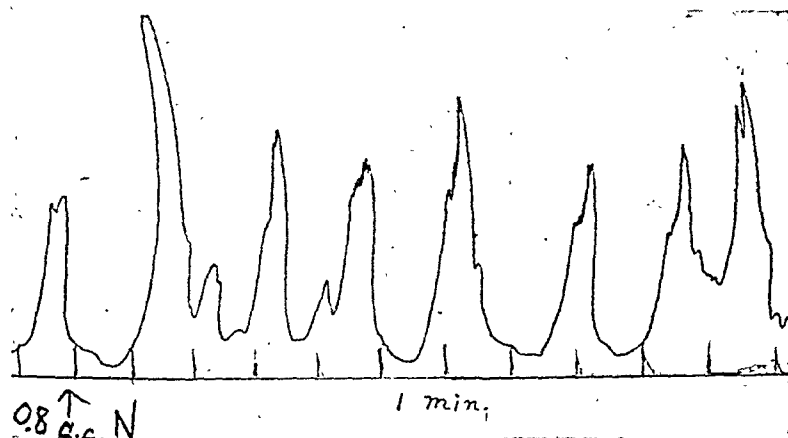


Fig. 3.—Tracing of uterine contractions in rabbit during the first day after delivery. Record made one hour after first dose of nembutal and at the time of second injection.

change in uterine contractions, but did slow the maternal respiration and suppressed fetal activity considerably.

4. Fetuses removed after the larger doses did not respond normally to stimulation and showed definitely depressed respiration.

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MALARIA COMPLICATING PREGNANCY

WITH A REPORT OF 27 CASES

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DURING the past twenty years in the city of Augusta, Georgia, of rather stable population of 65,000, 58 per cent of which are Caucasian and 42 per cent negro, there were approximately 27,300 live births, about 16,000 white and 11,300 negro. Among these were collected reports of 27 cases of malaria complicating the pregnancy. Twenty-two were in white and 5 in negro women. Most of the cases occurred in the 4 months of August, September, October, and November, each having from 4 to 7 cases. June and July had 2 and 3 cases, respectively, and the other months had one or none.

Age.—The youngest patient was a negress 15 years old and five months pregnant. She had 3 chills, recovered, and went home undelivered. Ten patients were under 21 years, 10 were 21 to 26 years of age and the others, all white, were 28, 32, 34, 35, 37, and 38, and the oldest 41 years of age.

Month of Gestation.—Two were in the first trimester, 8 in the second trimester, and 17 in the third trimester. All of this last group except one were eight months or more.

Type of Malaria.—Thirteen were tertian, 11 estivo-autumnal, 1 quartan, and 2 not determined because of incomplete records.

Symptoms.—Twenty patients had history of one to many chills, in some cases at very regular intervals. Many had malaise, headache, and dizziness. Few had vomiting and fainting attacks. Fever ranged from 100° to 105° F., but in each case it was promptly reduced by quinine therapy. One white woman near term was in coma for forty-eight hours and died. One negro woman in coma lived. In several patients, there was a marked degree of jaundice, and a large spleen was noted in many cases. Anemia by nature of the disease is common. Four patients had 1,000,000 red blood cells per cubic millimeter, 3 patients 2,000,000, and 2 only had more than 4,000,000 each. Leucopenia is also common. One patient had 3,000 to 4,000 white blood cells per cubic millimeter, 3 patients had 4,000 to 5,000, 2 patients 5,000 to 6,000, 2 patients 6,000 to 7,000, 2 patients had 7,000, one 8,000, two 9,000, three 10,000, two 11,000, one 12,000, one 13,000, and one 19,600. The hemoglobin corresponded with the number of red cells in each case. One had 10 per cent, one 20 per cent, one 30 per

change. Fetuses removed after six hours were rather inactive and responded slowly to strong stimulation. In these, respiration was slow and irregular at first, but gradually improved. No fetuses died during any of the experiments.

DOGS

Only two dogs were used, one having 9 and the other 6 fetuses just at term. The uterus and fetuses of one animal were observed for seven and one-half hours. During the first four hours of the experiment, this dog was given three doses of pentobarbital sodium, a total of 0.35 gr. per pound of body weight. Four fetuses were removed about the middle of the experiment and five more at the end. All were alive and active.

The second dog was observed for five hours. She was given two doses, a total of 0.2 gr. of pentobarbital sodium per pound during the first hour. The uterus continued to contract actively (Fig. 6). At the end of the experiment six fetuses were removed, one of these dead. The others soon became active. One pup out of each litter was bottle fed and kept alive.

DISCUSSION

In most of these experiments I also studied the behavior of the fetuses. A series of cinematographs were made of the fetal behavior during the experiments. It was observed that a dosage of 0.1 gr. of pentobarbital sodium per pound body weight did not alter the fetal behavior; but repeated doses would cause suppression of reaction to stimulation, gasping movements in utero or in the bath, and sometimes violent kicking was seen. During many experiments active peristalsis was observed and a number of animals defecated into the bath. On a few occasions actual delivery of fetuses occurred. Some of the guinea pigs and dogs removed by sectioning the uterus during or at the end of the experiment were kept and bottle fed.

In the experiments where 0.2 or 0.3 gr. of pentobarbital sodium per pound was administered, the fetuses became quite inactive and did not respond normally to various stimuli. During such experiments the near-term fetuses were put into a box with a light over them and in a few hours they became active. No mothers died from nembutal given in this series of experiments. Following the larger doses a few fetuses died in utero during the experiment.

The results in these experiments confirm the findings of Adair and Pearl,⁷ in that nembutal produced no appreciable change in uterine activity. The marked effect of nembutal on smooth muscle of the uterus, noted by Gruber⁸ was not observed. Unusual restlessness was not seen in any animals following various doses of nembutal. However this may be due to the fact that the series was not larger.

CONCLUSIONS

1. One dose of pentobarbital sodium (0.1 gr. per pound) did not cause a decrease in the tonus or the contractions of the uterus, when this viscus was kept relatively intact in the animal.
2. Fetuses remained active and responded to light stimulation with such a dosage.
3. Doses two and three times as large (0.2 to 0.3 gr. per pound), administered during a period of one to three hours, caused very little

In the second trimester of pregnancy 7 patients had malaria: 4 tertian, 1 estivo-autumnal, 1 quartan, and 1 not stated as to type. Two aborted during the attack and a third bled vaginally but went home undelivered. One negress with quartan type fever $4\frac{1}{2}$ months pregnant aborted after she had received 100 gr. of quinine over a period of four days. Three patients were pregnant at six months, one miscarried after ten days of illness, and the other two went home undelivered after recovery from the malaria attacks.

In the third trimester there were 18 patients; one at six and one-half months (tertian) aborted; one at seven months not delivered; one at seven and one-half months delivered prematurely; nine were at eight or eight and one-half months' gestation; six of these delivered spontaneously and 3 went home undelivered. Altogether there were 15 at eight months to term. Twelve delivered live babies, the largest 7 pounds 7 ounces and the smallest 3 pounds 5 ounces. The smallest one and probably another of these babies died before the mothers left the hospital. Three women went home undelivered but in good condition and with living fetuses. There was one maternal death after a stillbirth at term.

From this study the rule may be suggested that the danger to the fetus is greater the earlier in pregnancy that the attack occurs, but that the danger to the mother is greater if the attack is late.

ROLE OF THE PLACENTA IN MALARIA

A few studies in the more recent cases of malaria were made in regard to the placenta. These are few because delivery rather seldom took place during an actual crisis and often after the blood stream had been pretty well cleared of parasites. In those few cases (4), in which we were able to obtain the placenta at the height of the attack, the maternal red cells were loaded with parasites. Possibly on account of the relative stagnation of the maternal blood in the placental sinuses the placenta becomes a veritable storehouse similar to the spleen, and abortion or premature labor may be a protective measure. In no case have we* been able to establish the idea of transmission to the fetus by finding parasites in the fetal circulation of the placenta. Apparently from this study the cause of abortion or premature labor seems to be in the malarial attack itself more than in the therapy used, although quinine has the reputation of having oxytocic principles. Answer to the inquiry of just how the onset of labor is induced by malaria is not forthcoming. In every case where labor is brought on in association with a malarial attack, observation should be recorded as to whether uterine contractions occur first or vaginal bleeding is first, this with an effort to find out whether the fault lies in the uterine muscle or in the placental attachment. In every case in this series in which that was recorded, vaginal bleeding was first, and in one or two cases the patient recovered from this without aborting. Consequently, it is suggested that the lesions lie in the placental attachment, and that small retroplacental hemorrhages take place followed by uterine contractions and labor in those women who abort or have a premature labor.

SUMMARY

1. Malaria complicated pregnancy in this locality during a period of twenty years, once in 727 live white births and once in 2,260 negro livebirths recorded.

*In cooperation with Dr. V. P. Sydenstricker.

cent, one 40 per cent, three 50 per cent, four 60 per cent, six 70 per cent, and four 80 per cent in those recorded. More than one-half of the patients had albuminuria, usually in slight degree.

Therapy.—Almost all of the patients were treated with quinine, and it is of interest to note the oxytocic effects, if any, of quinine. The usual dosage was 20 to 30 gr. daily. The following 7 patients had large doses of quinine up to 300 gr. and not under 80 gr. without inducing labor:

1. Gravida, 6 months, 130 gr. in 7 days during attack of malaria. No abortion.
2. Gravida, 8 months, 180 gr. in 6 days. No premature labor.
3. Gravida, 5 months, 80 gr. in 8 days. No abortion.
4. Gravida, 6 months, 185 gr. in 9 days. No abortion.
5. Gravida, 7 months, 150 gr. in 5 days. No premature labor.
6. Gravida, 8 months, 200 gr. in 2 weeks without onset of labor.
7. Gravida, 8 months, 120 gr. and went home, recovered without onset of labor.

The subsequent patients were the only ones who had been administered quinine prior to the onset of labor, premature or at term:

1. Gravida, 8½ months, 80 gr. in 12 days. Premature labor, infant weighed 5 pounds 1 ounce.
2. Gravida, 8½ months, 30 gr. daily with onset of labor the second day.
3. Gravida, 5 months, 100 gr. over a period of 5 days before abortion.
4. Gravida, 7½ months, 280 gr. before premature labor. Child lived.
5. Gravida, 8 months, 300 gr. administered prior to onset of labor. Child lived.
6. Gravida, 6 months. Aborted after 7 to 9 days of tertian fever. Quinine probably had been given at home.
7. Gravida, 4½ months. Negress with quartan malaria. Aborted after 100 gr. of quinine given over a period of 4 days.
8. Gravida, 8 months. Premature delivery. Infant weighed 3 pounds 5 ounces, the mother had severe estivo-autumnal malaria with daily chills and coma. She received 20 to 30 gr. of quinine prior to delivery.

The following lists the 5 patients who aborted or had labor associated with an attack of malaria, but before quinine was administered:

1. White woman, aged 20 years, at term, estivo-autumnal malaria, comatose, died following delivery of stillborn infant.
2. Gravida, 6½ months, stillborn, labor before quinine given.
3. Gravida, 2 months, began to abort prior to administration of quinine.
4. Gravida, 4 months, aborted before treatment began.
5. Gravida, 8½ months, premature delivery during an attack of estivo-autumnal malaria before quinine was given.

Mortality.—One white woman, 20 years of age, pregnant at 8 months, and stricken with estivo-autumnal malaria, was in coma for two days and died after stillbirth.

The maternal mortality was about 4 per cent and the fetal mortality about 60 per cent.

In the first trimester, 2 patients had attacks of malaria, one tertian and one estivo-autumnal. The former aborted, the fetus dying probably before the administration of quinine. The other patient went to term and delivered a live baby in spite of a very severe prolonged attack (Case 1).

CASE 1.—White woman, aged 18 years, primigravida, became ill with estivo-autumnal malaria at three months' pregnancy and for four months she was recorded to have chills and fever daily. She had headache, dizziness, dyspnea, fainting attacks, and became extremely anemic, the lowest recorded red blood count being 1,090,000, white corpuscle count 7,500, and hemoglobin Dare 10 per cent. She lost weight to 87 pounds. She was treated by repeated transfusions totaling 3,000 c.c. and an aggregate of 350 gr. of quinine. In spite of all of this and two attempts to induce labor by castor oil and strychnine she continued pregnant to term, when she spontaneously gave birth to a healthy live baby weighing 7 pounds 2 ounces.

carry her child to term. It was anticipated that removal of the vaginal septum at the time of delivery would probably be necessary, and it was hoped that the nonpregnant uterus might not interfere too seriously with the mechanism of normal labor.

The patient was seen at regular intervals in the clinic, and except for a greater than average gain in weight (45 pounds) and recurrence on several occasions of the vaginitis previously noted, the pregnancy progressed normally until admission to the hospital at term on Feb. 7, 1940.

On admission, the patient was having contractions at intervals of five to six minutes, lasting thirty to forty seconds and was losing a moderate amount of amniotic fluid, the membranes having ruptured two hours previously. The McDonald measurement was 32 cm. and the fetus lay obliquely in the abdomen with the breech in the left iliac fossa and the head in the right upper quadrant. The fetal heart tones were regular and strong. On rectal examination the presenting part could not be determined; it was thought that the cervix lay in the left vaginal fornix and was dilated approximately 4 cm.

A flat plate of the abdomen revealed an apparently full-term pregnancy with the fetus presenting by the breech. X-ray pelvimetry by the method of Thoms gave the following diameters: Transverse diameter of inlet, 14.5 cm.; anteroposterior diameter of inlet, 10 cm. Laboratory examinations of urine and blood revealed nothing of significance.

During the twelve hours after admission the patient continued in active labor. Contractions occurred every two to three minutes and were moderately strong. One and one-half grains of seconal was given shortly after admission, and the same drug in a dose of 4.5 gr. was given about six hours later with only fair relief of pain. Vaginal instillation of a 1-1000 aqueous solution of zephiran (high molecular alkyl-dimethyl-benzyl ammonium chloride) was carried out every four hours, and the patient received an intravenous infusion of 500 c.c. of 10 per cent glucose in normal salt solution.

There was no evident progress of the labor and the fetal heart tones had gradually become more rapid, reaching a rate of 190 per minute. The patient's temperature had risen to 102.8° F. and examination of the nose and throat and of the chest disclosed nothing significant. Urinalysis remained entirely negative.

At this time a vaginal examination was made in order to determine the precise stage of labor and to discover, if possible, the cause of the dystocia. It was found that a larger vagina on the patient's left side and admitting two fingers easily was separated from a smaller vagina on the right side by a septum which extended from the vault to a point just inside the introitus. Two distinct, though somewhat poorly developed cervixes were found and two uteri could be made out. The pregnancy appeared to be in the right uterus while the left uterus, which was quite soft and approximately the size of a twelve to fourteen weeks' gestation, was empty. The left cervix admitted one finger and the right (pregnant) cervix barely a finger tip.

Lipiodol (15 c.c.) was introduced by means of a catheter into the left uterine cavity and an x-ray film was made. The report reads in part, "—apparently a bicornuate uterus, the pregnancy being in the right portion of the uterus." It might be added that no communication between the cavities is demonstrable (Fig. 1).

Cesarean section was advised because of the evident fetal distress (rapid heart) and because of the obstacle to engagement offered by the nonpregnant, left uterus and the probable rudimentary nature of the cervix and possibly of the uterine muscle.

A low cervical section was performed, using the double flap (Beck) technique. Anesthesia was gas-ether. The right uterus contained a full-term fetus. The uterus was markedly elongated, the musculature was poorly developed, and about 0.5 cm. in thickness. At the right side of this uterus were attached the round and broad ligaments, a tube in the normal position, and a normal ovary. The left uterus was about 5 by 7 by 9 cm., and at its left border it displayed the normal attachments. The left ovary contained several follicular cysts. The adjacent medial borders of the two uteri were devoid of attachment above the level of the vaginal vault.

After mobilizing an upper and lower peritoneal flap, the uterus was incised longitudinally in the lower uterine segment. A living, female infant was extracted by the breech. The placenta was attached in the posterior portion of the fundus and

2. With the youngest patient 15 and the oldest 41, three-fourths were under 26 years of age. Two-thirds were in the last trimester of pregnancy. It was more frequent in white women.

3. The symptoms were mainly those of recurrent high fever and anemia. Most were treated with quinine, and its effect in regard to pregnancy was studied.

4. The maternal mortality was about 4 per cent; fetal approximately 60 per cent. It seems that an attack of malaria is more fatal to the fetus if occurring early in pregnancy and more dangerous to the mother if occurring late.

5. The maternal blood of the placenta apparently becomes a storehouse for the malarial parasites, but in no case could we find them in the fetal blood.

PREGNANCY IN UTERUS DIDELPHYS*

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A BRIEF survey of the literature of developmental abnormalities of the uterus and its appendages leaves one with the impression that there is some confusion in the use of terms to describe the anomaly herewith presented. For that reason, it may be well to state at the outset that the term "uterus didelphys" is used as defined in Dorland's American Illustrated Medical Dictionary: "either of two distinct uteri occurring side by side in the same individual." In addition to this duplication of the entire uterus, the patient who is the subject of this report exhibited also a septate vagina with no demonstrable communication between the two canals.

At first thought one might consider this complete duplication of the birth canal an extremely rare occurrence. However, even an incomplete search of the literature of the past ten years discloses eleven such cases and the fact that at least four of these were not suspected until found at laparotomy or at autopsy necessitates the conclusion that the condition is present not too infrequently.

B. H., 22 years old, white, a primipara, applied for prenatal care in the Out-Patient Clinic of Firmin Desloge Hospital of St. Louis University on June 14, 1939. Past history was generally negative; there had been no operations. Family history was not significant. She had been married for two and one-half years with no previous pregnancy, and her husband was said to be in good health. The menstrual flow appeared at the age of 12, the menstrual periods had been regular every twenty-eight days, lasting seven days, and the flow was described as profuse. There had been severe abdominal cramps on the first day of each period. The last menstrual period had occurred two months previously on April 18, 1939. Physical examination disclosed the following: Weight, 127 pounds; blood pressure 95/60; pulse, 84 per minute; temperature, 98.6° F. Tenderness was noted in both lower quadrants, and bilateral, firm masses were described on either side of the midline just above the symphysis. Vaginal examination revealed the presence of a septate vagina and a severe vaginitis which made complete examination impossible. For this reason it could not be determined whether a double cervix was present or not. *Trichomonas vaginalis* was found in the discharge from the vagina. Pelvic measurements were as follows: spines, 25 cm.; crests, 31 cm.; E. C., 18 cm. bi-tuberos, 9 cm. Internal measurements could not be made because of the painful vaginitis. Treatment of the trichomonas infestation was instituted and a diagnosis of pregnancy in a uterus didelphys was recorded upon pelvic examination at a subsequent visit to the clinic. There are many instances recorded in the literature of women with double uterus who have been delivered without incident via the normal passages, and it was felt that this patient might well be given a trial labor, should she

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Administration of neoprontosil was begun immediately following operation, and after the second day, the patient received 60 gr. per twenty-four hours until the drug was discontinued on the eleventh day.

Transfusions of 1,000 c.c. of banked blood were given on the fifth and seventh postoperative days, the latter being followed by a severe febrile reaction. No urinary symptoms were noted.



Fig. 2.—Eight months post partum. Two distinct uterine cavities are visualized. Right tube not well outlined.

A small superficial wound abscess was evacuated on the sixth day, and all sutures were removed on the twelfth day. Involution of the right (pregnant) uterus was delayed, and on the twelfth day the fundus was 4 cm. below the umbilicus and slightly tender. It was impossible during the puerperium to follow the involution of the left uterus. It was noted that the lochia rubra was of a brighter than usual color and the amount was definitely more profuse than customary.

At the time of discharge from the hospital on the thirtieth postoperative day, mother and child were in good condition.

The patient was seen in the out-patient clinic on March 25, 1940, six weeks after delivery, and at that time the abdominal wound was completely healed, clean, and dry. Vaginal examination was impossible because of severe vaginitis and the accompanying discharge was positive for *Trichomonas vaginalis*. During the following four months I did not see the patient, though she continued to report to the

was removed. The uterus did not contract well despite the injection of oxytocics, and there was troublesome bleeding from the needle puncture sites during the closure of the incision in which three layers of No. 2 20-day chromic catgut were placed and in addition several mattress sutures for hemostasis. The previously mobilized peritoneal flaps were overlapped and the abdomen closed in the usual manner without drainage. Two ounces of zephiran (high molecular alkyl-dimethylbenzyl-ammonium chlorides in aqueous solution 1:2000) were poured into the peritoneal cavity before closure.

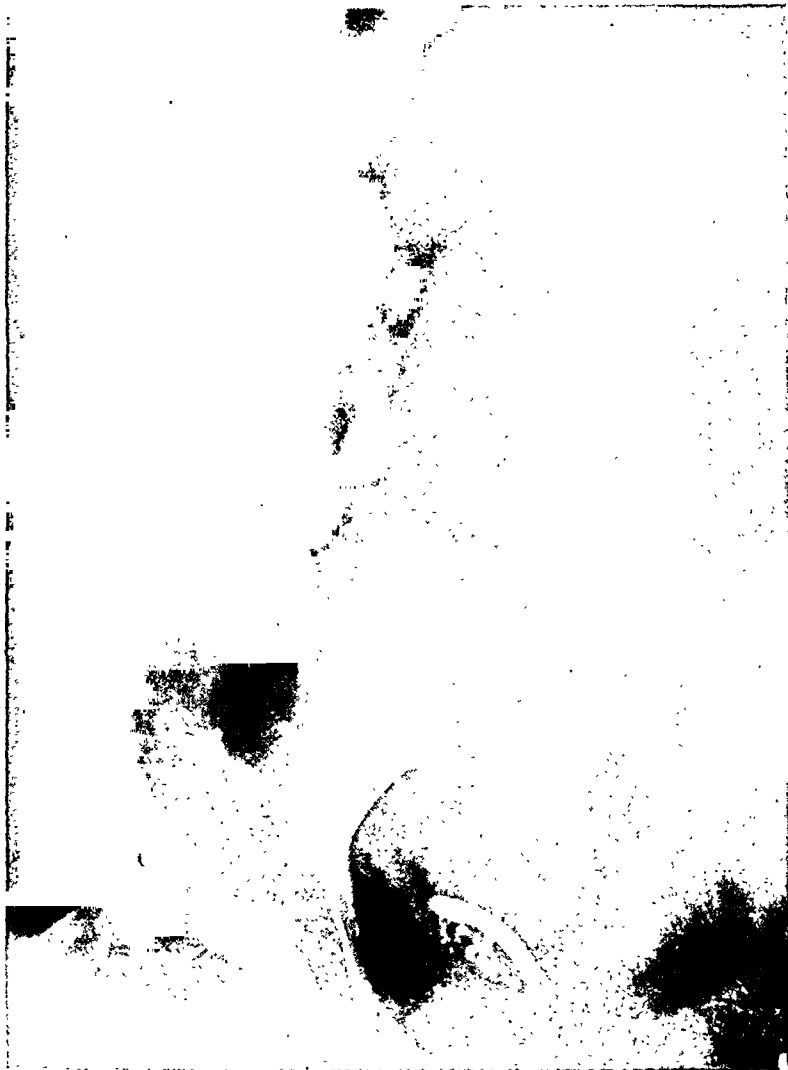


Fig. 1.—Fetus presents by the breech. Lipiodol has been injected into the nonpregnant uterus.

The immediate postoperative condition of the patient was fair (blood pressure, 110/80, temperature, 98.8° F., pulse, 180, good volume). She received a transfusion of 1,000 c.c. of banked blood (equivalent to 400 c.c. of whole blood) during closure of the operative wound.

The postoperative course was stormy during the first ten days. The temperature ranged from 100 to 102° F. except for a posttransfusional rise of 104.5 F. on the sixth day. The pulse remained rapid but of good quality. On the tenth postoperative day the temperature returned to normal and remained so thereafter.

The leucocyte count was never increased above the 8,700 recorded on the first postoperative day, and on the ninth day was 8,300 with a very slight shift to the left in the differential count. The red cells on the ninth day were 3,870,000 and the hemoglobin 11.3 gm.

INTESTINAL OBSTRUCTION COMPLICATING PREGNANCY*

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FIVE cases of intestinal obstruction complicating pregnancy have been seen at the Magee Hospital in 45,000 deliveries during the past twenty years. As they differ in many respects, these cases serve to emphasize that such complications are individual problems, requiring separate and distinct surgical and obstetric considerations in the management of each.

CASE 1.—Mrs. K. B., aged 21 years, para ii, six and one-half months pregnant, was admitted to hospital Dec. 25, 1930. Eight weeks previously this patient had undergone an appendectomy, at which time a mildly inflamed appendix kinked by numerous adhesions had been removed through a small McBurney's incision. A post-operative course of sixteen days was uncomplicated, and until three days prior to admission she had been free from abdominal pain.

At the time of admission the patient was seriously ill. She had been suffering with severe pain in the right side of her abdomen for three days. During that time she had vomited almost continuously and had not had a bowel movement for two days.

On examination the patient was very toxic and definitely dehydrated. The abdomen was distended and tympanitic, with spasticity and extreme tenderness over the entire right side. Temperature was 101° F.; pulse, 136; leucocyte count, 28,500. A diagnosis of acute intestinal obstruction was made, and the patient was prepared for immediate operation. Under spinal anesthesia a midline incision above and below the umbilicus was made. The abdominal cavity contained 500 c.c. of turbid fluid. Two thick bands of adhesions were found at the base of a loop of terminal ileum, and at this point the enclosed intestine was tightly constricted. This entire loop, which measured 12 cm. in length, was gangrenous. The fibrous bands were divided, and 18 cm. of ileum were resected. A side-to-side anastomosis was performed and drainage was secured through a stab wound in the right flank. The midline incision was closed. Several times during the operation the patient vomited fecal fluid.

Following operation the temperature rose rapidly to 106° F.; pulse was 160. The abdomen presented signs of generalized peritonitis. Supportive measures were employed, but the patient died twenty-four hours after operation. An autopsy was not performed.

Delay in surgical intervention is unquestionably the greatest factor contributing to this unfortunate outcome. In this respect, this patient's history is typical of many of the mortalities reported. Quite often this factor is not within the power of the surgeon to correct, and this suggests the need for earlier hospitalization of gravid patients presenting any part of the symptom complex of partial intestinal occlusion, particularly in the presence of an abdominal scar.

CASE 2.—This is a report of intestinal obstruction in pregnancy, due to volvulus.

According to Kornfield and Daichman only one case of volvulus complicating pregnancy had been reported in the United States up to 1934. A rather careful search of the literature showed no additional such instance to date. This second case seems somewhat unusual in this respect.

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clinic for treatment of her vaginitis which showed, however, no improvement following the use of various antiparasitic preparations and the prescription of an acid douche. It is interesting to note that this failure of treatment was apparently due to a failure to recognize the necessity for proceeding against the invading parasite in both vaginas. The various interns who saw the patient had made a strenuous effort to eradicate the infestation in the larger (left) vagina but had neglected the smaller right cavity which acted as a reservoir. After explaining to the patient the technical difficulty involved and teaching her to insert a suppository and later the douche tip in each side following careful insufflation of each vagina, the vaginitis cleared up and with it the discharge. Neither has recurred up to the present time.

On Oct. 10, 1940, the patient was readmitted to the hospital for further study. Under morphine and hyoscine analgesia a pelvic examination was made. The vaginal mucosa was normal in appearance; there was no discharge and no vaginitis. Bimanual examination disclosed the right vagina to be narrow but deep, admitting one finger. The right cervix was about 2 cm. in length, moderately firm and the external os closed. The right uterus could be palpated and was carrot-shaped, freely movable and apparently about 7 cm. in length. The left vagina admitted two fingers easily; the cervix was extremely short, being only a button-like protrusion in the vaginal vault. The left uterus could not be definitely outlined.

A Ferguson speculum was introduced into the right vagina and a soft rubber catheter (No. 18), threaded onto a stylet, was passed into the right uterine cavity. The Ferguson speculum was then removed and a bivalve speculum placed in the left vagina, and an olive-tipped metal cannula was introduced into the left uterine cavity. A total of 12 c.c. of an opaque medium was then injected into each cavity and an x-ray film was exposed. The roentgenologist's report reads in part as follows, "—opaque medium is visualized in the peritoneal cavity. There seems to be some dilatation of the left tube. The right tube is not well visualized." To this may be added the remark that the complete duplication of the uterus with entire absence of communication between the two cavities is well demonstrated. The reason for failure to visualize the right tube, of course, lies in the technical difficulty involved in injecting both uteri simultaneously. The size of the right vagina and the close proximity of the two cervixes would not permit the passage of two metal cannulas equipped with olive tips, and some of the injected medium had escaped from the right uterus alongside the soft catheter (Fig. 2).

SUMMARY

A case of uterus didelphys with complete septate vagina is reported in which pregnancy occurring in one uterus was terminated by cesarean section because of dystocia. The dystocia was brought about by inability to dislodge the nonpregnant uterus which blocked the inlet to the pelvis.

Pregnancy may have occurred as a result of internal migration of the spermatozoa. This presumption is based on the fact that pregnancy occurred in the right uterus while coitus was obviously possible only in the left vagina, there being no demonstrable communication between the two vaginas. It is, of course, possible that external migration of the sperm from the left to the right vagina may have occurred.

Vaginitis, resulting from trichomonas infestation, was a complicating factor during the postoperative period. It was very resistant to treatment until measures were taken to insure that not only the insufflation carried out in the clinic but the patient's self-treatment at home was directed simultaneously to both vaginal cavities.

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power, 34.3 per cent; chlorides, 453, mg.; urea, 10.3 mg.; urinalyses, negative. With the administration of morphine and hot abdominal stupes, the paroxysmal character of the abdominal pain subsided and the vomiting ceased after six hours. While it was felt that this patient probably had a partial intestinal obstruction due to post-operative adhesions, the appearance of such improvement seemed to warrant a conservative form of management, along with constant and careful observation. Accordingly, the sedation and hot abdominal stupes were continued and the patient was given daily high colonic irrigations. Clear liquids were given by mouth on the second day. Improvement continued and she was discharged after four days. A non-residue diet was prescribed, and she was seen weekly throughout the remainder of her pregnancy. On several visits attacks of abdominal "cramps" were described, each of which had been relieved by enemas.

On Sept. 18, 1938, this patient was readmitted and a third classical cesarean section was performed. The Fallopian tubes were ligated, and several intra-abdominal adhesions involving the uterus, omentum, and small intestine were divided. The patient had an afebrile and uncomplicated puerperium. After returning to normal life, she continued to have occasional attacks of abdominal pain which, however, were relieved within a few hours after taking an enema. Recently these attacks have become much less frequent and much less severe, due in part at least to a more careful and intelligent management on the part of the patient.

CASE 4.—Mrs. A. F., aged 26 years, gravida ii, eight and one-half months pregnant, was admitted to the hospital Feb. 3, 1940. She complained of severe pain in the right side, vomiting, and marked weakness.

Her pregnancy had been uneventful until 5:00 A.M. on the day of admission, when she was awakened by a sharp pain in the right lower quadrant, referred to the mid-lumbar region. Vomiting followed in two hours, and was repeated five times prior to admission. In 1925 she had had an exploratory laparotomy because of abdominal pain associated with the history of having swallowed a fishbone. Her appendix was removed at that time, and she had not complained of any abdominal symptoms until the onset of the present illness. Her first pregnancy in 1938 was uncomplicated, and terminated in the spontaneous delivery of a normal child.

Examination showed a moderately obese white female lying in bed, moaning and rolling from side to side. She complained of a constant stabbing pain in the right lower quadrant and held her right leg flexed upon her abdomen. Her skin was pale and moist. Temperature was 97° F. and pulse 100. The abdomen was moderately distended, and there was an old irregular right rectus scar, extending from the iliac spine to the costal margin. Marked tenderness was present below the angle of the incision. Peristalsis was present on the left side and absent on the right. The uterus showed no evidence of irritability. The presenting part was not engaged. Fetal heart sounds were 140. The cervix was not dilated nor effaced. The leucocyte count was 12,300; polymorphonuclears, 90 per cent; lymphocytes, 10 per cent; red blood count, 3,440,000; Hb., 58 per cent. Chlorides were 363 mg.

It was felt that this patient had developed a mechanical intestinal obstruction due to adhesions at the site of previous laparotomy, and with evidence of impending shock, cesarean section with prompt release of the obstruction was indicated. A classical cesarean section was performed, using gas-local anesthesia, and a living child was obtained. Exploration of the right side of the abdomen, following closure of the uterus, revealed numerous fibrous bands and adhesions which, along with pressure from the enlarged pregnant uterus, had caused marked distortion of the contour of the ascending colon and cecum. At one point in the ascending colon a moderate-sized fecal impaction was broken up. Then various adhesions and fibrous bands were individually clamped, cut, and ligated. Immediately following operation the patient was given 500 c.c. of citrated blood, and was placed on the Ochsner peritonitis regime. Within the first twenty-four hours postoperatively, she developed a marked paralytic ileus, which was managed successfully by Wangenstein drainage. There was a septic febrile reaction, with the temperature reaching 103° F. and pulse 124, on the third day. This fell steadily to normal levels by the sixth day.

Mrs. A. S., aged 24 years, gravida i, was admitted April 5, 1929. She was four months pregnant. Her chief complaints were nausea, continuous vomiting, and intense abdominal pain. Seven years previously a right inguinal herniotomy and appendectomy had been performed through a single incision. In the past two years she had been troubled with constipation. Since the onset of pregnancy this symptom had become more severe, and she began having periods of nausea and vomiting associated with attacks of abdominal pain.

All these symptoms increased in severity in the two weeks prior to admission, and on arrival at the hospital, she was suffering with intense pain, localized to the right lower quadrant. There was marked abdominal distention and tympany. The lower right side was exquisitely tender. Temperature, pulse, and respirations were not elevated. Immediate operation was advised.

Under spinal anesthesia the abdomen was opened by a right rectus incision. The abdominal cavity contained 300 c.c. of thin serosanguineous fluid. The terminal ileum was enormously distended. One darkly discolored loop of bowel, measuring 20 cm. in length, was twisted upon itself at a point 2.5 cm. from the ileocecal valve. This twist was easily corrected, inasmuch as there were no constricting nor adjoining adhesions. Immediately, the gas in the obstructed portion of the bowel was liberated, with improvement in the color and appearance of the terminal ileum and its mesentery. The uterus, enlarged 6 cm. above the symphysis, showed no abnormalities. The abdomen was closed without drainage.

Following operation the abdominal distention subsided. After the fourth day the patient was having normal bowel movements. She was discharged on the twenty-fifth day. Except for occasional periods of nausea and vomiting, she remained well throughout the remainder of her pregnancy, and was delivered by midforceps of a normal infant at term. This patient's subsequent history showed that she remained free from symptoms suggestive of recurrence of intestinal obstruction. A second pregnancy was uneventful throughout.

A supravaginal hysterectomy was performed eleven years later because of profuse metrorrhagia. It was interesting to observe that there were no adhesions involving the intestinal tract, although a pale firm area of scarring about the ileum at the site of the previous vulvulus was seen.

Undoubtedly the time of operation was a very important element in this patient's successful recovery. It is reasonable to assume that further delay may have permitted irreversible damage to the twisted loop of bowel, altering definitely her postoperative course.

CASE 3.—The following is a report of partial intestinal obstruction occurring in pregnancy, which, with careful observation, was amenable to conservative management:

Mrs. C. D., aged 26 years, gravida v, was admitted July 26, 1938. She was six and one-half months pregnant and complained of severe cramplike abdominal pains, nausea, and vomiting. Her past medical history showed that in addition to two abortions she had had two classical cesarean sections, one in 1934 and the second in 1935. Each section had been indicated because of a cephalopelvic disproportion, and at each operation the abdomen had been entered through a left rectus incision. There was no history of sepsis following the termination of each of these four pregnancies, and the period of convalescence had in each instance been uncomplicated.

To this patient the appearance of abdominal pain, nausea, and vomiting of such severity in the latter months of pregnancy was an entirely new and unprecedented occurrence. Shortly after admission the abdominal pain became localized to the left side. Examination at this time disclosed a moderately distended abdomen. There was marked tenderness over the left lower quadrant and the abdominal muscles were tense. Peristalsis was not prominent but there was an occasional loud gurgle suggestive of fluid in the presence of trapped gas. The uterus was relaxed and the fetal heart rate was 140. The temperature was 100; pulse, 104; white blood count, 7,400 with 76 per cent polymorphonuclears; 24 per cent lymphocytes; CO₂ combining

In retrospect, this patient's first attacks of pain were probably due to an attack of acute appendicitis which went on to rupture and abscess formation. Fortunately, the patient was able to wall off this infection satisfactorily, and even further to acquire a degree of immunity to organisms within the abscess. The absence of fever and leucocytosis were probably important reasons for not suspecting an infectious process.

This case also illustrates that conservative management of partial intestinal occlusion may be employed to excellent advantage. It serves to show, however, that constant observation, preferably with hospitalization, is extremely important if the patient is to receive the benefit of prompt surgical intervention when it is indicated.

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CALCIFIED FIBROMYOMAS

REPORT OF 4 CASES

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SINCE the reports of Peacock¹ and Wang,² there has been no mention of calcified fibromyomas in the available literature. During the last eight months (January to October, 1940) we have encountered 4 cases presenting calcification occurring in fibromyomas. During this period of time 23 hysterectomies were performed in which fibromyomas were the operative indication in 20, carcinoma of fundus in 1, and diffuse endometrial polyps in the other 2 cases.

A consideration of the 4 cases showing calcified fibromyomas is in order, and the case reports are herewith given:

CASE 1.—M. F., colored, female, widow, aged 52 years, gravida 0, was admitted to the hospital with the chief complaint of abdominal pain. Pain began twenty-four hours before admission without prodromal symptoms. The onset was sudden, forcing the patient to lie down because of a "faint feeling." This was followed by a chill, abdominal enlargement, with exquisite abdominal tenderness, nausea, and vomiting following intake of food or fluid. In the past history the patient was seen at the age of 48 years with fibromyomas of the uterus, causing pain in the right flank; surgical intervention was refused at that time. Physical examination on this admission revealed an obese negro female with a temperature of 99.2° F., pulse 76, respirations 20, and blood pressure 194/100. The heart was enlarged, with the left border dullness being 2 cm. to the left of the midclavicular line, and there was a soft systolic murmur over the apex.

The abdomen was obese and there was exquisite tenderness with rebound phenomenon throughout. There was a hard tumor mass palpable in the left hypochondrium which was not movable. Pelvic examination revealed the pelvis filled with a hard nodular tumor mass. The white blood count was 14,300 with 6 stabs, 80 neutrophils, 8 monocytes, and 6 lymphocytes. Sedimentation time was 46 and 80 mm. for the first and second hours, respectively. At operation a large, extremely firm mass, measuring 18 cm. in diameter, was found lying in the left mid-abdomen, and when delivered was attached by a pedicle 10 cm. in length to the uterus at the

Enemas were effectual, with return to normal evacuation on the eighth day. The remaining postoperative course was uneventful.

The *fifth case* is interesting in that at operation an old appendiceal abscess was encountered, which had not been suspected, although the patient had been under observation for several weeks.

Mrs. C. H., a colored female, aged 35 years, gravida vi, seven and one-half months pregnant, was admitted to the hospital July 17, 1940. She was suffering with intermittent attacks of midabdominal pain, which she insisted on associating with a bad fall four weeks previously. At a local hospital the abdominal pains, at that time, and on subsequent visits were dismissed as being due to pressure from the enlarged pregnant uterus. The abdominal pains continued and she began to vomit. Distention and obstipation followed. At the time of admission she had passed no formed stool for two weeks. Recently she had had diarrhea with passage of considerable flatus.

Her past medical history disclosed that she had been given two courses of anti-syphilitic therapy. There had been one miscarriage and four full-term pregnancies, all terminating normally.

On examination the abdomen was markedly distended and tympanitic. Peristalsis was quiet except for an occasional rush, which was then associated with pain, and definite tenderness, localized to the midline just above the umbilicus. The uterus was not contracting. The fetal heart sounds were 144. The initial laboratory work showed red blood count, 3,160,000; Hb., 63 per cent; white blood count, 7,500; polymorphonuclears, 63 per cent; lymphocytes, 37 per cent; nonprotein nitrogen, 27.5 mg.; sugar, 71 mg.; chlorides, 462 mg.; sedimentation time, 10 minutes, CO₂ combining power, 45.7 per cent; serology, negative; urinalyses, negative. It was felt that this patient had a partial intestinal obstruction, mechanical in type, with the etiology obscure.

She was given morphine at regular intervals, 2,000 c.c. of 5 per cent glucose in normal saline by vein daily, frequently repeated tidal wave enemas, hot abdominal stupes, and nothing by mouth. Within forty-eight hours definite improvement was noted. The distention became less and the vomiting ceased. After four days she was passing large quantities of liquid stool and was given a soft nonresidue diet.

Two weeks after admission a gastrointestinal series showed a partial bowel obstruction in the midileum, probably due to adhesions. Repeated blood counts showed no evidence of leucocytosis. There had been no elevation of temperature or pulse.

Twenty-nine days after admission the patient's membranes ruptured spontaneously, and after an hour and sixteen minutes of fairly hard contractions, she was delivered spontaneously of a normal four and one-half pound living infant. An afebrile post-partum course ensued.

On the twelfth post-partum day, a severe pain appeared in her right lower quadrant, followed by a steadily increasing abdominal distention, as well as a rather marked nausea and a mild degree of shock. There was marked tenderness in the right lower quadrant. As these signs and symptoms persisted with increasing severity, laparotomy was advised.

On opening the abdominal cavity, an old appendiceal abscess was encountered, extending from the cecum along the right side of the pelvic cavity to the cul-de-sac. One fecalith was found. There were adhesions of small bowel to the abscess, and in several places the small bowel was sharply angulated, forming a partial obstruction. The right Fallopian tube was enlarged and adherent to the mass. The appendix was not located. The adhesions were separated to relieve the obstruction, and the right Fallopian tube was removed. Three drains were placed in the abdomen before closure.

The patient was placed on peritonitis regime. She maintained a temperature near 101° F. with a pulse of 100 until the ninth day when the temperature and pulse returned to normal following removal of the drains. After the sixth postoperative day, she retained a soft diet and had normal bowel movements. She was discharged from the hospital Sept. 22, 1940, after sixty-seven days of hospitalization. Her condition was very good.

CASE 3.—S. W., a colored female, 35 years of age, gravida iii, para i, was admitted to the hospital because of menorrhagia and metrorrhagia, lower abdominal pain, and backache. These symptoms have been present intermittently the last two years. Past history reveals that two years before patient had a hard palpable uterine tumor reaching to the umbilicus, causing pain and tenderness in both adnexa on palpation. Examination on this admission revealed a well-nourished, colored female, whose only positive findings were in the abdomen. Here a nodular, firm mass was palpable, reaching midway between the umbilicus and xiphoid process. There were no other palpable masses. Pelvic examination revealed the cervix displaced forward and the uterus involved in the large abdominal mass described above. This mass was wedged into the pelvis but was movable. The adnexa were not palpable. Urinalysis was within normal limits. Hematologic survey revealed a hemoglobin of 7 Gm. and 2,500,000 erythrocytes. Sedimentation rate was 26 and 56 mm. for the first and second hours, respectively. Kahn was 0-0-0. Following transfusions a supracervical panhysterectomy was performed, bilateral salpingo-oophoritis being present. The postoperative course was somewhat stormy, with the patient developing right bronchopneumonia on the fifth postoperative day. She was discharged from the hospital twenty days postoperatively.

Pathologic Description.—*Gross:* Specimen consisted of a markedly enlarged, deformed uterus with both tubes and ovaries attached. The uterus roughly covered an area of 30 cm. in diameter and was so twisted and distorted by multiple fibroids that it was impossible to obtain accurate measurements. The fibroids were intramural, submucous, subserosal, and pedunculated. They varied from millet seed to 11 cm. in diameter. On sectioning there were two intramural fibroids which showed deposits of calcium around their peripheries and scattered indiscriminately through the centers. These measured, respectively, 3 and 8 cm. in diameter. The endometrial cavity had lost its normal outline and was encroached upon by numerous fibroids. The lining endometrium showed scattered hemorrhages but no polyps were seen. The Fallopian tubes showed marked stretching, kinking, and distortion by virtue of the growth of fibroids. The ovaries were bound to the tubes by fibrous tissue and showed small cysts beneath the surface. No corpora lutea were seen. *Microscopic:* Sections were composed of large masses of fibrous tissue, running in varying directions and cut on different planes. Scattered throughout were fragments of muscle cells. The areas of fibrous tissue proliferation were encapsulated and at the periphery showed large areas of hyaline degeneration in which there occurred a deposition of calcium material. There was no uniformity of pattern demonstrable in the calcium deposits after thorough study. At first glance it appeared to be deposited in cartilaginous tissue; however, further study showed that the lacuna-like formations were the results of the surrounding hyalinized fibrous tissue, shrinking from the occasionally recognizable fibroblast nuclei. There was no histologic evidence of malignancy seen in the sections studied. Sections of the uterus with endometrium attached showed endometrial hyperplasia with small cyst formation. The endometrium overlying the fibroids showed atrophy with edema and hemorrhages. Sections of Fallopian tubes showed the classical chronic obliterative salpingitis. The ovary showed numerous small follicular cysts and a thick covering membrane. No corpus luteum cysts were seen. *Diagnosis:* Multiple uterine fibromyomas, calcification, chronic salpingitis, chronic oophoritis, follicular cysts, endometrial hyperplasia, endometrial atrophy (pressure).

CASE 4.—H. H., white female, aged 45 years, gravida iv, para iv, was admitted with chief complaint of vaginal bleeding. This bleeding had been present for the past year with periods lasting two to three weeks and causing great weakness. The past history was negative. Patient was married and had four children, the oldest 26 years and the youngest 12 years of age. Examination was essentially negative with the exception of the pelvis. Pelvic examination revealed the uterus enlarged, smooth, and hard, filling the pelvic outlet. The adnexa could not be outlined. The cervix showed bilateral tears. Urinalysis was within normal limits and hemograms revealed 8 Gm. of hemoglobin with 3,670,000 erythrocytes. Sedimenta-

right broad ligament. The pedicle was twisted and had caused some torsion of the uterine fundus, and the uterus and fundus were surrounded by omentum. The adnexa were normal to gross examination. Because of the patient's hypertension, a subtotal hysterectomy was deemed inadvisable and the tumor with the pedicle was removed. Patient was discharged fifteen days later, following an uneventful postoperative course.

Pathologic Description.—*Gross:* Specimen consisted of a mass of hemorrhagic, irregular, nodular, stony-hard tissue, measuring 19 cm. in diameter. There was a mesenteric adhesion and a twisted 2 cm. pedicle attached. On sawing through the mass, it was composed of dense, hemorrhagic fibrous tissue with calcium deposits scattered throughout. Prior to sectioning, x-rays were taken showing a diffuse calcification. *Microscopic:* Sections consisted of hyalinized fibrous tissue, containing large amounts of calcium deposited throughout. Scanty traces of muscle tissue were seen, and there was marked extravasation of blood in some areas. The vascular supply was interesting in that the vessels were surrounded by calcium deposits frequently. The vessels were, however, patent, being gorged with erythrocytes now. In areas capillary rupture was seen accounting for the hemorrhage visible grossly. There was no histologic evidence of malignancy or organized bone formation. *Diagnosis:* Uterine fibromyoma, pedunculated, calcified, twisted.

CASE 2.—E. J., colored, female, aged 52 years, gravida ii, para ii, was admitted with pain in the lower right quadrant of the abdomen. It was accompanied by nausea and vomiting on two occasions. Pain was described as being severe, intermittent, and there was residual tenderness in the lower right quadrant and right flank. There were no urinary symptoms. *Past medical history:* Twelve years prior to admission the patient was seen in this clinic at which time she had acute pelvic inflammatory disease with a 3-plus Wassermann reaction. Menses ceased six years ago without difficulty. Physical examination revealed temperature 99.0° F., pulse 88, respirations 16, and blood pressure 150/90. Examination was essentially negative, with the exception of the abdomen which was protuberant, particularly in the lower portion. There was marked tenderness in the lower right quadrant and over the right flank. There was no tenderness in either costovertebral angle. Rebound tenderness was referred to the lower right quadrant; there was no muscle rigidity. Pelvic examination showed a lacerated, eroded cervix. The fundus of the uterus could not be definitely outlined although no masses were palpable. Motion of the cervix caused no pain. Urinalysis was essentially negative. White blood count was 11,600 with 9 stabs, 50 neutrophils, 35 lymphocytes, 5 monocytes, and 1 basophile. Sedimentation rate was 17 and 40 mm. for the first and second hours, respectively. Kahn was 3-2-2. Patient was operated upon three hours after admission, and the appendix, when delivered, showed no gross abnormality. Limited exploration was carried out through the incision, and a pedunculated, subserous, uterine fibroma the size of a golf ball was found on the right side which was removed. Patient was discharged eight days later following an uneventful convalescence.

Pathologic Description.—*Gross:* Specimen consisted of a round mass of fibrous and muscle tissue, measuring 3.5 by 3 cm. It showed at one point a break in the continuity of the serosal covering which resembled the point of amputation. To palpation it was generally doughy, resilient, and palpable within its substance were numerous, hard calcified areas. On sectioning, the cut surface was arranged in whorls and bundles whose centers were chalky yellow and hard, gritty to palpation. There were no areas of hemorrhage or liquefaction seen grossly. *Microscopic:* Sections consisted of muscle and fibrous tissue arranged in bands and bundles cut in varying planes. The vascular supply to this structure was rather small and the vessels showed intimal proliferation and occlusion in areas. There were large areas of fibrous tissue, containing lacuna-like structures around which were seen deposits of calcium. These represented viable fibroblast nuclei whose cytoplasm had for the most part undergone collagenous and hyaline changes with calcium deposition occurring there. In the sections studied there was no histologic evidence of malignant degeneration. *Diagnosis:* Subserous, pedunculated fibromyoma, calcification.

symptoms inasmuch as acute interstitial hemorrhage is seen in the sections, yet no muscle cells and only a few scattered fibroblast cells are seen. By far the greatest portions of the sections are composed of deposits of calcium in an indeterminate supporting stroma. This stroma in the immediate vicinity of the now thrombosed arteries and veins assumes the character of acellular fibrous tissue resembling that

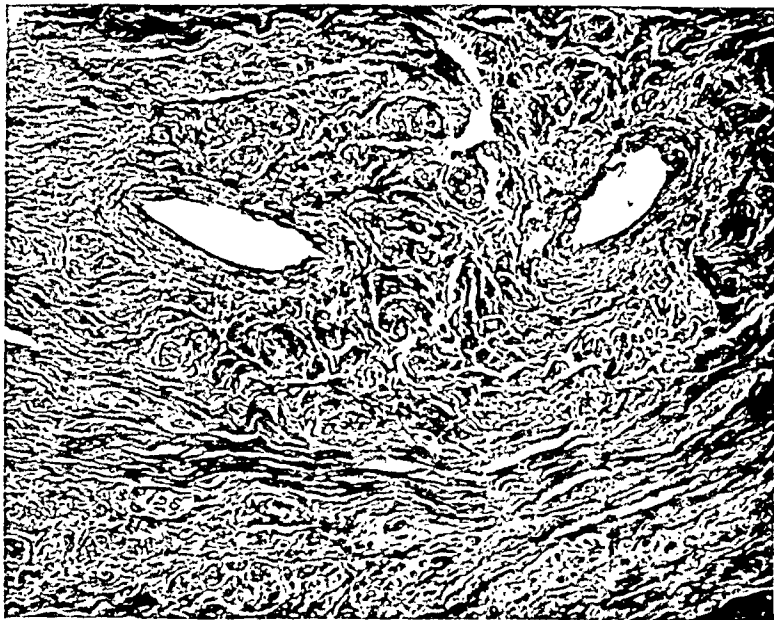


Fig. 1.—Early fibroblast proliferation causing compression and atrophy of the muscle cells. Note the intact vascular supply.



Fig. 2.—Fibroblast cells showing condensation and formation of collagen which in areas shows early hyaline changes.

seen in keloids. This is interesting in view of the finding of 3 of the cases of calcified fibroids occurring in negroes. None of the above cases show external evidence of keloid formation and in our experience here we have encountered only one case of keloid formation occurring in conjunction with fibromyoma of the uterus.

tion rate was 18 and 42 mm., first and second hours, respectively. Serology was 0-0-0. She was given preoperative transfusions of blood, and a supracervical hysterectomy was performed. The adnexa were grossly normal. The postoperative course was uneventful, and the patient was discharged eleven days postoperatively.

Pathologic Description.—*Gross:* Specimen consisted of uterus, containing a low uterine fibroid. The uterus and fibroid measured 20 by 18 by 10 cm. On sectioning the endometrial cavity was distorted and compressed by the low uterine fibroid, and the lining endometrium was hemorrhagic. There were no polyps seen grossly. Sectioning of the fibroid showed a 1.5 cm. well-circumscribed area of calcification. There was no other gross evidence of retrograde change seen. *Microscopic:* Sections of uterus with endometrium attached were taken through the point where the fibroids were compressing the endometrial cavity and showed marked stretching of the endometrium and narrowing of the layer, the whole being accompanied by edema and scattered, diffuse hemorrhages. The endometrium was atrophic here, although in other areas it was in the late secretory phase, showing occasional scattered basal cyst formations. Sections of fibroids revealed classical bands and bundles of fibrous tissue cut on varying planes. In the area described grossly as being partially calcified, there was seen to be a hyaline degeneration of the collagenous fibrous tissue with deposition of calcium indiscriminately throughout this area. There was no evidence of osteogenesis. *Diagnosis:* Uterine fibroids with calcification, late secretory endometrium, endometrial cysts.

DISCUSSION

The average age of these patients varied from 35 to 46 years. Three of them were negroes; 1, although married, had never been pregnant, the other 3 had had 2, 3, and 4 pregnancies, respectively. One of the patients showed chronic salpingitis and chronic oophoritis with follicular cysts. Two of the patients had normal adnexa, and in the other patient the adnexa could not be explored due to the limited surgical incision. Bleeding and pain were marked symptoms in the 2 patients showing intramural fibroids with calcification. In the 2 cases of pedunculated fibroids, there was no bleeding, and in 1 case (M. F.) there was pain which was probably due to torsion of the uterine body; a case similar in some respects to this one was reported by Roberts.³ The other patient (E. J.) had unexplained, right-sided pain, which did not recur postoperatively, although no gross lesions were found in the abdomen that could in any way account for the symptoms. The fibromyoma was removed incidental to appendectomy which on gross and histologic examination was normal.

In studying the histology of the fibromyomas from those showing little or no retrograde changes to the one (M. F.) showing almost complete calcification, one is impressed by the sequence of changes as portrayed in sections taken from various lesions. The earliest change is one of proliferation of fibroblast cells between the muscle cells, causing minor compression and atrophy of the muscle cells (Fig. 1). In other areas of the same section one finds almost complete absence of muscle cells and a marked condensation of the fibroblast cells which in areas assume a collagenous aspect (Fig. 2). Careful scrutiny of the vessels in this region reveals no evidence of occlusion or destruction. The next change encountered is one of hyalinization of the collagenous bundles and dense fibrous tissue with the loss of the small interstitial capillaries and venules, this being followed by the deposition of calcium in the intensely hyalinized areas and occurring without any apparent relationship to the larger vessels. The lesions are found immediately surrounding the arteries and also at considerable distances from the visible arteries in the sections. The arterial wall in the majority of instances shows no remarkable medial or intimal changes. The deposition of calcium, once established, could not be seen to be dependent upon any local condition, occurring as it does scattered throughout the hyalinized collagenous tissue, and in places so surrounding viable fibroblast nuclei that at first glance they give the appearance of lacunae formation. In one case (M. F.) the vascular supply must have been adequate up to the onset of the acute

sible until the vertex was dislodged and pressure removed from the urethra by vaginal manipulation. The cervix was now found to be about 7 cm. dilated. A thick anterior lip of cervix was incarcerated between the head and the symphysis. The cervix was forced above the symphysis after displacing the vertex. With this manipulation, a small amount of foul smelling meconium-stained amniotic fluid escaped.

Twenty-four hours after admission contractions were weak and infrequent. Labor was stimulated by minim doses of pitocin. A few hours after the pitocin had been given the patient became quite dyspneic. Respirations were quite deep and 52 per minute. The marked costovertebral tenderness persisted. Intravenous Hartman's solution alternately with glucose was given. Twenty-nine hours after admission she was having strong uterine contractions and the vertex was distending the perineum. While preparing the patient for delivery, contractions stopped again. A vaginal examination revealed vertex in A.P. diameter and no cervix palpable. Pressure on fundus was not sufficient to force vertex over the scarred perineum. A pudendal nerve block was done and forceps were applied. By intermittent tractions the vertex was brought over the perineum without doing an episiotomy through the scarred perineum. The forceps were not removed until after the head was delivered. Following the delivery of the shoulders and with the delivery of the trunk, a small piece of tissue protruded through the vagina.

A foul smelling stillborn male infant weighing 6 pounds 12 ounces was delivered. The placenta was expressed from the vagina twenty minutes later. During the third stage of labor, an estimated blood loss of about 500 c.c. was sustained. The uterus contracted well following administration of intravenous ergometrine. Following delivery of the placenta, a long loop of tissue was seen protruding through the vagina. Examination by palpation revealed it to be attached to the cervix posteriorly, and with the palpation one end came free. Because of the infected field, the attached end was tied off at the base and the remainder cut free. No further bleeding resulted.

The detached cervical tissue was 27 cm. long and 2.5 cm. wide. It had a raw purplish red appearance. The border representing the external os was rather smooth while the detached border was irregular. Microscopic examination showed marked extravasation of blood into the tissue substance. There was little cellular structure present, and only in an occasional area was any glandular structure found.

After delivery the patient was given a transfusion of 400 c.c. of blood.

On the first post-partum day, she was stuporous, respirations 40 per minute; pulse, 104 and of good quality; and temperature, 102.4° F. An x-ray of the chest revealed small areas that were interpreted as infarcts or atelectasis. Oxygen was given by nasal catheter.

The patient was critically ill for four days and then began to improve slowly. On Sept. 2, 1939, a repeat x-ray of the chest showed clearing of the areas previously involved. Treatment for the most part was supportive, involving fluids, transfusions, and oxygen. Eighty grains of sulfanilamide were given for two days, and then reduced to 60 gr. for two days, but then discontinued because of marked anemia.

Three weeks after admission the patient was well enough to be discharged. Speculum examination revealed a nonsymptomatic rectovaginal fistula on the left wall of the vagina about 1 cm. above the mucocutaneous junction. The cervix was raw in appearance, bled easily, and was practically flush with the vaginal vault. The posterior lip presented three linear grooves running anteroposteriorly. The fundus was about 3 cm. above the symphysis.

The patient was seen again six weeks later, at which time the cervix looked scarred and gray and still bled very easily. Skin tests revealed negative tuberculin and Ducrey reactions. Frei reaction remained positive for ten days. She attended a venereal disease clinic regularly where she was given sulfanilamide.

The patient presented herself at the prenatal clinic on June 17, 1940, with the history of amenorrhea since Feb. 18, 1940. Examination of the abdomen revealed a soft tumor mass arising from the pelvis and extending to within 5 cm. of the umbilicus. Vaginal examination revealed this to be a pregnant uterus. The cervix

It is seen from the above that no common denominator for the determination of the degenerative changes of calcification can be arrived at in an analysis of the predominating signs and symptoms or in an examination of the pathologic findings of these four cases.

SUMMARY

1. Four cases of calcified fibromyomas are presented. Two cases (pedunculated subserosal) presented signs and symptoms of an acute surgical abdomen. Two cases (intramural) were found in routine pathologic examination and presented the usual symptomatology of fibromyomas.

2. The calcium deposition centers predominantly in areas where collagen has become partially hyalinized regardless of the condition of the vascular supply.

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ANNULAR DETACHMENT OF THE CERVIX

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SPONTANEOUS amputation of the cervix is a rather infrequent complication of labor. The literature reveals only 32 cases, and of these, only 3 are reported in American periodicals. This is a case of spontaneous cervical amputation in which the patient recovered after a prolonged convalescence, and fourteen months later delivered a normal premature infant in the thirty-third week of gestation.

History.—A. C., a colored primipara, 30 years of age, was admitted to Gallinger Hospital on Aug. 24, 1939, after having had an irregular type of labor for about twenty-one hours. She had a hard chill about four hours before admission. Membranes had ruptured seven hours before admission. Last period began on Oct. 6, 1938, making the expected date of confinement July 13, 1939. She had attended prenatal clinic regularly since her sixth month of pregnancy and had received antisyphilitic therapy. She had had a rectal stricture for the past several years which had been dilated on two occasions, and on admission she gave no history of difficulty with bowel action.

Physical Examination.—Temperature was 101.2° F.; pulse, 104; and blood pressure, 130/80. Her skin felt hot and dry. The abdomen revealed a uterus at term undergoing regular firm contractions every fifteen minutes, lasting only a few seconds. The infant was in L.O.T. position with fetal heart sounds in L.L.Q., 164 per minute. The head was well engaged. Marked right costovertebral tenderness was present. Examination of the perineum revealed marked scarring and induration.

Rectal examination revealed a stricture about 4 cm. above the sphincter which had an orifice of about 2 cm. On vaginal examination the vertex was found in L.O.T. position. Cervix was thick and 4 cm. dilated. Diagnoses of lymphopathia venereum with rectal stricture, right pyelitis, and term pregnancy were made.

Laboratory Data.—Blood count revealed Hg 40 per cent (Newcomer): red count, 3,300,000; white count, 20,000. Urinalysis showed 3+ albumin, numerous white blood cells, and a few granular casts. A positive Frei reaction was obtained.

Progress.—Patient was given intravenous glucose and morphine, and an hour after admission she had a hard shaking chill and became quite dyspneic, but improved with further morphine sedation. Eight hours after admission the patient was out of labor and resting fairly comfortably. Fifteen hours after admission her bladder was quite distended and no fetal heart could be heard. Catheterization was impos-

size. One lobe was located centrally, over the internal os, while the other lobe was situated over the right anterior lateral surface of the uterus in the lower uterine segment. The umbilical cord was centrally attached to the centrally located lobe, and there were several blood vessels traversing the distance between the two lobes. The patient ran a fairly comfortable postoperative course, the temperature fluctuating between 100° and 101° F. up to the ninth postoperative day, and then returning to normal. She was discharged on October 20, 14 days postoperatively, in good condition, with a healthy female infant.

MISSED ABORTION, WITH A NEGATIVE FRIEDMAN TEST, FOLLOWING MADLENER OPERATION

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FAILURE of an approved type of sterilization operation which has been properly performed is always of interest. When the pregnancy also involves diagnostic difficulties such as lack of subjective symptoms and a negative Friedman test, it probably warrants reporting.

A white woman, aged 27 years, gravida iii, para iv, was referred to Steiner Clinic by her physician, who suspected a fibromyomatous uterus with irregular bleeding. Her family history was of no significance, except one sister was in an institution for the feeble-minded. Menstruation began at the age of 14, was of the twenty-eight-day type, and lasted four days without unusual discomfort. Her first pregnancy in February, 1935, resulted in the birth of normal triplets. The second pregnancy was complicated by placenta previa with hemorrhage and was terminated by one of us (B. L. S.) by a classical cesarean section at Georgia Baptist Hospital in October, 1939. A Madlener operation was done on both tubes, using silk ligatures, and her convalescence was uneventful.

Her last normal menstrual period occurred about six months ago. There had been no period of amenorrhea, but she had experienced irregular bleeding varying in amount from "spotting" to a rather steady flow with only an occasional interval of a few days. There was no pain, change in appetite, breast signs, or increased frequency of urination. Slight nausea had been present for the past six weeks.

Examination showed nothing of interest except in the abdomen and pelvis. The low right paramedian scar was intact. A nontender, slightly movable mass arose from the pelvis and reached the abdominal wall about 7 cm. above the symphysis pubis. Bimanual examination showed a parous outlet with good muscular support. The urethra and Bartholinian glands were normal. The vagina contained a moderate amount of sanguinomucoid discharge which issued from the cervix. The cervix was soft and patulous and pointed toward the introitus. The uterus was enlarged to about 10 by 12 cm. and of somewhat softer than normal consistency. The adnexa could not be palpated and there was no tenderness in the fornices.

A diagnosis of pregnancy with threatened abortion was made but the patient demurred on account of the lack of subjective symptoms which had been quite pronounced in her previous pregnancies. A Friedman test was then done using two 7.5 c.c. doses of concentrated urine. Laparotomy on the rabbit at thirty-six hours was definitely negative (both ovaries studded with mature but unruptured follicles). The blood sedimentation rate, blood count, urinalysis, and Kahn test were normal. In view of the diagnostic evidence against pregnancy, laparotomy was advised.

At operation on Aug. 15, 1940 (G. A. W.), the uterus and abdominal scars were found to be adherent and loops of small intestine and omentum were attached to each side. The uterus was the size and consistency of a three months' pregnancy but was of nongravid appearance. No corpus luteum or mature follicles could be

was firm and irregular and flush with the vaginal vault. Her pelvic measurements were I.S. 24 cm., I.C. 26 cm., E.C. 19 cm., and D.C. not reached. Outlet was ample.

The patient reported to prenatal clinic regularly. She was admitted into the hospital Oct. 3, 1940, having been in intermittent labor for a period of fifty hours, with a history of ruptured membranes fifteen hours prior to admission. She was thirty-three weeks pregnant. Five and one-half hours after admission, a boy infant weighing 3 pounds 9 ounces was delivered as a footling breech. Labor and delivery were uncomplicated and the infant was in good condition. She was discharged in good condition after a normal post-partum course. Urinalysis on admission revealed 3+ albumin, and numerous pus cells and hyaline and granular casts. She had no urinary symptoms. On discharge hyaline and granular casts were still present. The blood picture and chemistry were normal as was the kidney dilution and concentration test.

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CENTRAL PLACENTA PREVIA WITH ACCESSORY LOBE

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WE ARE presenting a rather rare anomaly of the placenta, the association of central placenta previa with placenta succenturiata. We have been unable to find a similar case in the literature.

B. L., a 26-year-old primipara, was admitted on Oct. 5, 1940, with a history of moderate vaginal bleeding, unassociated with pain, for the week prior to admission. Her last menstrual period was Jan. 11, 1940, and the expected date of confinement was Oct. 18, 1940. The patient had been married for five years, but had never been pregnant previously, despite the fact that she used no contraceptive measures. The cause of the sterility was found, upon investigation, to be due to a spermatozoal deficiency in her marital partner. The present pregnancy had been induced by artificial insemination of a donor's semen on her calculated ovulatory date, which occurred approximately between January 22 and January 24, as estimated by basal body temperatures and vaginal smears. Past medical and surgical history were essentially negative. The ante-partum course was normal. Membranes were intact.

Admission examination revealed a uterus enlarged to the size of a thirty-eight weeks' gestation, which contained a full-term fetus in the right occipitoposterior position. The fetal heart was in the right lower quadrant, with a rate of 140 and was regular. On rectal examination, the cervix was found to be one finger dilated. The vertex was high above the pelvic brim. During the examination, blood continued to ooze in small amounts from the vagina, and the patient was considered not to be in labor. Subsequent rectal examination showed a soft, thickened mass overlying the lower posterior position of the cervix. X-ray examination showed, after the instillation of sodium iodide into the urinary bladder, a wide spacing between the presenting fetal head and the concave superior border of the bladder, suggesting a central placenta previa. On the basis of this radiographic evidence, substantiating clinical impressions, abdominal termination of the pregnancy was deemed necessary.

On October 6, a low-flap transverse cesarean section was performed under local anesthesia and a living female infant, weighing 6 pounds 4 ounces was delivered. The placenta was found to consist of two distinct lobes of approximately the same

DIAPHRAGMATIC HERNIA COMPLICATING THE PUERPERIUM*

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A HERNIA through the diaphragm occurs rarely, but, due to the position of the abnormal opening, is much more likely to be exposed to the force of increased abdominal pressure in labor than is an inguinal hernia, which is protected by the bulk of the uterus. This combination of diaphragmatic hernia and the immediate puerperium is sufficiently uncommon to merit the report of the following case: (An exhaustive survey of the literature brought to light only a single reference in the *Journal of the American Medical Association* of 1937 under "Query and Minor Note," the case of a doctor's wife whose labor and puerperium were complicated by herniation into the thorax of one-fourth of her stomach.)

Our patient, a 20-year-old white gravida ii, first presented herself when three and one-half months pregnant. Her last normal menstrual period was on Aug. 25, 1939. She was considered to be at term on June 2, 1940. The pertinent history obtained was a right inguinal herniorrhaphy at Billings Hospital in 1938, four months following a normal spontaneous delivery at Chicago Lying-in Hospital. Physical examination was essentially negative; Wassermann reaction was negative. Her pregnancy, which was of forty-three weeks' duration, was marked by excessive weight gain (29.5 pounds) and albuminuria. The labor came on June 27, 1940 and after thirteen and one-third hours terminated spontaneously in the birth of a 9-pound female baby. A midline, second degree laceration was repaired under pudendal block anesthesia.

Immediately after delivery, the patient complained of left upper quadrant pain but was otherwise comfortable and in good condition. For the next seventeen hours she had mild lower abdominal pains, at the end of which time her pulse, temperature, respirations, and blood pressure were normal. Nothing unusual was detected by careful physical examination. When next seen, about sixteen hours later, she complained of severe left upper and lower quadrant colicky pains, of having vomited 5 or 6 times, and of obstipation. Physical examination was again negative and her pulse, temperature, and respirations were still normal. The possibility of an intestinal obstruction was suggested. The patient was closely watched. Early on the third post-partum day about fifty-some hours after delivery, with temperature 98.6° F. and pulse 100, signs developed which led to a clear-cut diagnosis. There were left-sided abdominal pains, tenderness, and slight distention. Examination of the chest revealed diminished diaphragmatic excursions and decreased breath sounds on the left. Typically intestinal borborygmus was heard high in the left axilla. The vomiting had ceased but the obstipation remained. The patient was admitted to the Chicago Memorial Hospital on July 1, 1940, with the diagnosis of intestinal obstruction on the basis of left-sided diaphragmatic hernia.

She was given fluids parenterally, and her symptoms rapidly subsided. However, the next day when fluids were given orally, the pain and vomiting re-appeared. Relief was obtained from morphine and atropine, and she remained asymptomatic throughout her hospital stay. Her pulse and temperature were always normal but for the first day's elevation of 100.4° F. Laboratory findings were negative but for occult blood in the stool on July 3. The patient left voluntarily July 10, but she agreed to return at a later date for operation.

*Presented at a meeting of the Chicago Gynecological Society, December 20, 1940.

found in either ovary. The Fallopian tubes showed the silk ligatures of the Madlener operation to be in situ and there was no sinus formation visible to the naked eye. A supravaginal hysterectomy was done and in spite of the temptation to study the shortened tubes, it was thought that the ovarian vascularity would be preserved best if these were not removed. An incidental appendectomy was performed.

Pathologic Examination (Dr. E. L. Bishop).—The uterus was filled with placental tissue and contained a degenerated fetus 8 cm. long. The uterine wall was thick and fibrous but no fibromyomas were found. The endometrial surface was obscured by placental tissue.

Microscopic Examination.—Sections of the uterine wall showed thick muscle and connective tissue bundles with some edema and vascularity. No fibromyomatous formation was seen. The endometrium was of gravid type and the decidua was thick and compact. There were several small necrotic areas in the decidual layer but no massive degeneration.

Sections of the placental tissue showed marked variation in the size and shape of the villi. All were covered with epithelium. The central cores showed varying changes, some fibrous, some loose and vacuolated, but no actual necrosis. Proliferating Langhan's cells and a few syncytial giant cells were seen.

Sections of the appendix showed the lumen filled with feces and an intact mucosa. There was some increase in connective tissue in the submucosa.

Diagnosis.—Uterine fibrosis with pregnancy. Degenerative changes in placental villi and necrosis of decidua. Gross degeneration of fetus. Chronic appendicitis with stasis.

COMMENT

The Madlener sterilization operation leads all others in popularity; but its silk ligatures in the presence of crushed tissue, where they will almost invariably cut through into the mucous membrane of the tube, violate two of the accepted principles of the use of this material, and sinus formation must occur frequently. Failures are difficult to estimate but they have been reported to be as high as 5 per cent.¹ The Pomeroy-Lull operation in which catgut is used without crushing is statistically more effective, but is much newer.

The Friedman test properly done is of inestimable value in the diagnosis of a pregnancy obscured by atypical objective and subjective symptoms, but it is dependent upon the presence of functioning chorionic tissue. Missed abortion is one of its recognized limitations but fortunately is not very common. In this case parietal and visceral adhesions interfering with uterine expulsive efforts may have been an etiologic factor in the missed abortion. The complete retrogression of the corpus luteum of pregnancy was also significant.

REFERENCE

(1) *Dippel, A. L.*: Surg., Gynec., & Obst. 71: 94, 1940.

384 PEACHTREE STREET, N. E.

a T-shaped end measuring 12 mm. in width. The lower or female jaw has a rectangular slotted opening that measures 7 mm. in width and 3 mm. in length, and the upper, solid, male rectangular punch blade measures about 6.75 mm. in width and 2.75 mm. in length. The male blade is invaginated into the female jaw by means of a lower shaft which is slotted to insure proper aligning of the jaws. The jaws may be opened wide like a scissors ordinarily, but for biopsy purposes they are opened 12.5 mm. or 0.5 inch.

This punch is capable of obtaining biopsies from either the right lateral wall or the left lateral wall, or the vault of the vagina. The punch takes a small side bite of folded tissue which opens to a size 3 mm. square, or a bite of folded tissue from the vault which measures 7 mm. in width and 6 mm. in length. These specimens include all the layers of the vaginal mucosa, and are about 1.5 mm. thick.

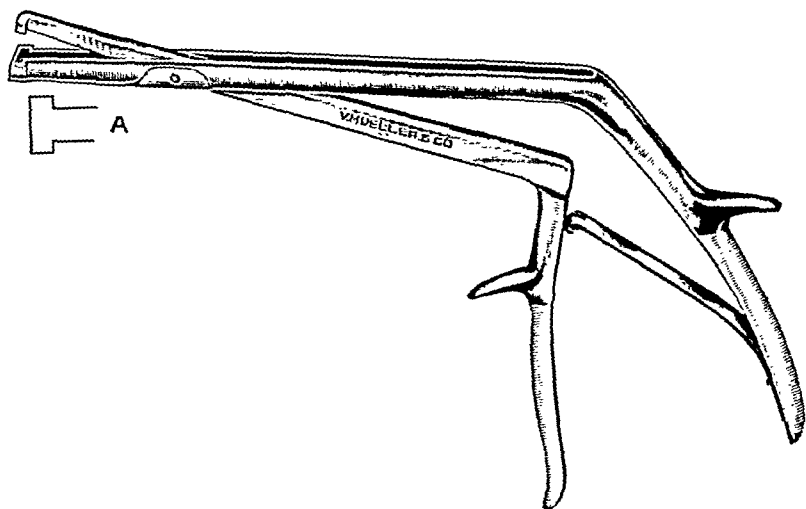


Fig. 1.—Three-way scissors type vaginal biopsy punch. (Courtesy of V. Mueller and Company.)

Technique.—The usual bivalve vaginal speculum is inserted so that the vaginal walls are a little lax. The site of the biopsy is sterilized by the usual antiseptics and then is injected with a small amount of 0.5 per cent novocaine producing a small bleb. The syringe and needle remain in situ thereby steadying and elevating the biopsied area, so that the biopsy may be easily obtained by applying the side of the three-way vaginal biopsy punch.

Very little pressure is necessary to obtain these specimens. As a rule with this procedure, especially with the 3 mm. square specimens, there is very little bleeding or pain. The specimen may be easily removed by picking it out with a tissue forceps or removing it with the detachable spring basket.

I wish to express my appreciation to Dr. M. Edward Davis for his suggestions.

REFERENCE

- (1) Maryan, H. O.: AM. J. OBST. & GYNEC. 36: 707, 1938.

30 NORTH MICHIGAN AVENUE

INTERSTITIAL TWIN PREGNANCY*

E. W. FISCHMANN, M.D., CHICAGO, ILL.

MRS. S. S., 39 years old, one child 22 years old, living and well, no other pregnancies, menses of the twenty-eight-day type, regular up to July 1, 1940, on Aug. 17, 1940, experienced moderate abdominal cramps unassociated by nausea and vomiting, frequent urination and moderate vaginal bleeding which had continued up to the time of examination.

Sept. 3, 1940, examination revealed patient in good physical condition, no abdominal rigidity, uterus was slightly enlarged and softened and the right ovary was palpable. Aschheim-Zondek test was weakly positive. A diagnosis of probable intrauterine pregnancy was made.

Patient returned on Sept. 30, 1940, and upon examination the uterus was found to be somewhat smaller and firmer with a hen egg-sized elongated cystic mass on the left side, and the right ovary was palpable and cystic. Patient had a moderate reddish brown vaginal discharge. Hemoglobin was 80 per cent; 4,100,000 erythrocytes; 11,000 leucocytes.

A diagnosis of probable left-sided interstitial pregnancy was made and the patient entered the hospital, and a laparotomy was performed. Upon opening the abdominal cavity, there was about 100 c.c. of hemorrhagic fluid, and the omentum was adherent to the hemorrhagic enlargement of the left horn of the uterus. A supravaginal hysterectomy with bilateral salpingo-oophorectomy was performed. The patient made an uneventful recovery.

Pathologic Report.—Specimen consisted of a corpus uteri, both tubes, and both ovaries.

The corpus uteri measured 8 by 6 by 5½ cm. It was deformed by a soft mass occupying its left horn; this mass measured about 4½ cm. in diameter, and on cut section contained clotted blood in the midst of which was a twin pregnancy, the length of the fetuses being 10 mm.

Both tubes were patent and of normal size except the interstitial portion of the left one which took part in the mass described above.

The ovaries were normal except that the right one contained a hemorrhagic corpus luteum cyst, measuring 5 mm. in diameter.

58 EAST WASHINGTON STREET

A THREE-WAY SCISSORS TYPE VAGINAL BIOPSY PUNCH†

HARRY O. MARYAN, M.S., M.D., CHICAGO, ILL.

IN A previous paper¹ I described my scissors type cervical punch for obtaining adequate biopsies of the cervix uteri. Subsequently I have also found this type of a punch with its modified jaws to be applicable for obtaining vaginal biopsies with ease.

This vaginal punch (Fig. 1) consists of a pair of handles with a spring and roller attachment, a shaft with a mortise or Bruening lock, and male and female blades. The shafts are long enough having an overall measurement of 18.5 cm., so that they can reach well into the vaginal vault. Beneath the female jaw there is attached the removable basket spring which retains the specimen. The handles are so aligned that the object is always in direct line of vision. The spurs on the handles prevent the hand from slipping when pressure is applied. The jaws present

*Presented at a meeting of the Chicago Gynecological Society, January 17, 1941.

†Presented at a meeting of the Chicago Gynecological Society, December 20, 1940.

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF JANUARY 21, 1941

The following paper was presented:

The Technique and End Results of Elective Fundal Cesarean Section. Dr. Edward A. Schumann.

MEETING OF FEBRUARY 18, 1941

The following papers were presented:

The Advantages of Conservative Obstetrics as Shown by Examination Six Weeks Post Partum. Drs. H. Bristol Nelson and Daniel Abramson. (For original article, see page 800.)

Statistics for Cesarean Section Throughout the State During 1939. Dr. Robert L. DeNormandie.

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL
SOCIETY*MEETING OF DECEMBER 2, 1940*

The following papers were presented:

Intestinal Obstruction Complicating Pregnancy. Drs. C. J. Barone, H. A. Power and C. L. Kuhn (by invitation). (For original article, see page 890.)

Pregnancy Complicating Breast Carcinoma. Drs. H. A. Power and J. M. Cook (by invitation).

ST. LOUIS GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 12, 1940

The following papers were presented:

Endometriosis of the Lungs. Dr. John E. Hobbs, and A. R. Bortnick. (For original article, see page 832, November, 1940 issue.)

Pregnancy in Uterus Didelphys. Dr. Joseph A. Hardy, Jr. (For original article, see page 885.)

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF DECEMBER 10, 1940

The following papers were presented:

Cord Transfusions at the Time of Delivery With Suggestions as to Their Use.

Dr. Harry W. Mayes.

Vitamin K Administered to the Mother During Labor as a Prophylaxis Against Hemorrhage in the Newborn Infant. Drs. Alfred C. Beck, E. Stewart Taylor, and R. F. Colburn. (For original article, see page 765.)

Urinary Stress Incontinence. Its Relation to Cystocele and Lacerations of the Pelvic Floor. Dr. J. W. Davies. (By invitation.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 20, 1940

The following papers were presented:

Diaphragmatic Hernia Complicating the Puerperium. Drs. S. T. DeLee and B. I. Gilson. (For original article, see page 904.)

Jelly Contraceptives. Drs. Irving F. Stein, Melvin R. Cohen, and Rita Nielsen, R.N. (For original article, see page 850.)

Sickle-Cell Anemia in Pregnancy. Drs. Alfred J. Kobak, P. J. Stein, and A. F. Daro. (For original article, see page 811.)

A Three-Way Scissors Type Vaginal Biopsy Punch. Dr. Harry O. Maryan. (For original article, see page 905.)

MEETING OF JANUARY 17, 1941

The following papers were presented:

A Study of the Corpora Lutea and the Endometria in Patients With Uterine Fibroids. Drs. John I. Brewer and Harold O. Jones. (For original article, see page 733.)

Nerve Tumors of the Female Generative Organs. Dr. Robert Meyer, Minneapolis, Minn. (By invitation.)

Interstitial Twin Pregnancy. Dr. E. W. Fischmann. (For original article, see page 905.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 6, 1940

The following papers were presented:

Anoxia Following Nitrous Oxide Anesthesia for Labor. Drs. Thomas R. Turino and H. R. Merwarth. (For original article, see page 843.)

Further Observation of Human Refrigeration. Dr. Temple Fay (by invitation).

Of the 6 cases of chronic malaria the drug was first used in the second, sixth, and the seventh month, in one each, and during the ninth month in the 3 remaining cases. In the 4 patients with acute malaria, the drug was given in the puerperium in 2 patients and in the fifth and sixth months of pregnancy in the other 2 patients.

The total dosage varied from 52 c.c. to 230 c.c. The author does not offer any specific routine for use of the drug except to mention that in 2 patients it was given in 2 to 3 courses, each of 4 to 5 injections; 7 c.c. in each of the first course, and 13 c.c. in each of the last course in one case; and daily injections for 3 courses in another case, amount dependent on blood findings. The remaining patients were treated throughout the remainder of their pregnancies and, or, into their puerperium.

In 2 cases the author, immediately post partum, utilized Frey's hysterotonographic method to check the effect of the drug upon uterine tonus. He found that following intravenous injection of tartrated antimony, the uterine muscle tone was increased and slowly returned to its previous tone.

He mentions that in considering the choice and dosage of this drug during pregnancy one must take into account this increase in muscle tone and its possible effect upon the fetus. He feels, however, that his dosages were within the limits of safety.

CLAIR E. FOLSOME.

Sodeman, W. A.: Cardiac Changes in Pregnancy Unrelated to Usual Etiologic Types of Heart Disease, *Am. Heart J.* 19: 385, 1940.

The author observed 73 apparently normal patients during pregnancy to ascertain what cardiac changes resulted from the gravid state. Palpitation or dyspnea or both developed in 31 and was sufficiently severe to constitute a complaint. Choking or "smothering" at night was complained of by two. Soft systolic murmurs were common and, at times, were markedly affected by posture. In 30 instances soft, short, transient, systolic pulmonic murmurs were heard. The heart was definitely beyond the midclavicular line in 12 cases; it was confirmed by x-ray examination in 10. Tachycardia was recorded graphically in 47 cases and ectopic beats in four. Edema of the ankles was present in 28. The blood pressure of every patient remained within the normal range. In 7 of the 73 patients symptoms and signs sufficient to suggest heart disease developed in the last trimester. In five of these, palpitation and dyspnea on exertion were accompanied by accentuation of the pulmonic second sound, extension of the left border of cardiac dullness beyond the midclavicular line and systolic apical murmurs, and in two by basal systolic murmurs, edema of the ankles and coarse râles at the bases of both lungs. The arterial pressure was within the normal range in all patients. In each instance delivery was uneventful, and examination during the puerperium disclosed that practically all the signs and symptoms had disappeared. So-called gestatory heart disease must be differentiated from organic heart disease as patients with the former type require no special treatment. The inclusion of patients with gestatory heart "disease" in the organic group not only causes them unnecessary expense, inconvenience, and worry but exposes them unnecessarily to added obstetric risks.

J. P. GREENHILL.

Clahr, Klein, and Greenstein: Rheumatic Heart Disease in Pregnant Women, *New York S. J. M.* 40: 1242, 1940.

The establishment of the prenatal cardiac clinic at the Morrisania City Hospital has led to a threefold increase in the number of diagnosed cases of rheumatic heart disease in pregnancy. The routine treatment of cases of rheumatic heart disease in pregnancy is described.

The combination of adequate bed rest and digitalis has been the most effective means in the prevention of intra-partum and post-partum cardiac failure in rheumatic heart disease. The only maternal deaths occurred in patients who had neither adequate bed rest nor digitalis.

J. P. GREENHILL.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Pathology of Pregnancy

Spector, H. I.: Marital Tuberculosis, *Am. Rev. Tuberc.* 40: 147, 1939.

Marital tuberculosis in this paper designates clinical tuberculosis in both husband and wife, not implying that the disease has been transmitted from the one to the other.

Spector's study considers available literature, 208 questionnaires answered by physicians in the U. S. and various foreign countries but is chiefly based on the histories of 210 tuberculous couples found among over eleven thousand cases of tuberculosis reported to the St. Louis Health Division.

Some of the final conclusions drawn by the author are the following: Marital tuberculosis is not as infrequent as is generally believed, amounting to 3.8 per cent of the reported cases of tuberculosis in married people. The majority of physicians answering the questionnaires approve of marriage between tuberculous individuals and between a tuberculous and nontuberculous one. The majority of phthisiologists permit their arrested married tuberculous patients to have children.

HUGO EHRENFEST.

Dodds, Gladys H.: Chronic Nephritis in Pregnancy, *Proc. Roy. Soc. Med.* 33: 737, 1940.

Chronic glomerular nephritis is predominantly a disease of young people, yet it is rarely associated with pregnancy. The incidence at the University College Hospital (London) was 1 in 1,100 deliveries. Clinical diagnosis of the disease, especially differentiation from a chronic hyperpiesis, is difficult, often takes much time, occasionally a year or more after delivery.

Remote prognosis for the mother is usually regarded as extremely unfavorable. If it is true that pregnancy is always liable to cause an exacerbation of the disease and shortens the patient's life, then obviously the best course to adopt is to terminate the pregnancy as soon as it is diagnosed. Only in exceptional cases gestation could be continued under proper medical treatment until the fetus has reached viability.

HUGO EHRENFEST.

Bertino, Steffano: Treatment of Malaria in Pregnancy with Tartrated Antimony, *Ginecologia* 5: 362, 1939.

The author treated 4 patients with acute and 6 with chronic malaria during pregnancy and the puerperium with intravenous administration of 1 per cent solution of tartrated antimony.

In all cases the disease was easily controlled. The hemoglobin increased 10 to 40 per cent and good health returned. One patient experienced vomiting and a few moments of severe coughing during the administration of the drug. The patient also showed restriction of urinary output. These untoward symptoms compelled interruption of treatment with tartrated antimony and resumption of administration of quinine, intramuscularly and by mouth.

Eight of the 10 patients were able to nurse their infants. Live babies were obtained in 9 cases. The end result of labor in one case is not reported. The initial weight loss of the infants was regained in normal length of time.

when glucose is given and the blood sugar concentration thereby returned to normal. However, the authors' experience with infants born of diabetic mothers has given them reason to question whether or not the hypoglycemia so frequently observed in these infants is as significant in the production of symptoms as is generally supposed.

In the past three years six infants born to mothers with diabetes have been cared for on the Pediatric Service at Yale University from the time of birth to their discharge. All six had very low concentrations of blood sugar during the first day or two of life. In three infants symptoms and abnormal findings were present. In no case was the administration of glucose effective in relieving the symptoms. More striking than the lack of response to glucose was the fact that in each of these infants evidence of organic disease was found which better explained the symptoms and clinical course than would the hypoglycemia.

J. P. GREENHILL.

Evans, John R., and Bouslog, John S.: Intractable Heartburn of Pregnancy, Radiology 34: 530, 1940.

In this report the authors show roentgenologic evidence of the so-called intractable heart burn of pregnancy. The etiologic factor is an esophageal orifice hernia. Due to a deficiency in embryologic development, there may be a congenital weakness of the esophageal ring, and, as in an inguinal hernia, later on in life, through trauma, or an increase in intra-abdominal pressure, a definite hernia may develop. The latter condition holds true in gravid women. The symptoms are constant and of increasing severity. The symptoms in nongravid individuals vary from vague nonspecific ones to those of abdominal or severe thoracic distress. Most patients exhibit various combinations of belching, heart burn, nausea, regurgitation, and vomiting. As pregnancy progresses the only relief obtainable is by maintenance of the upright posture. The symptoms bear no relation to the degree of gastric acidity and relatively little relief is obtained in these cases from antacids. Dilute hydrochloric acid does not aggravate the symptoms. Ulcer diets are disappointing, and the giving of salines and pyloric relaxants produce little or no change.

WILLIAM BERMAN.

Urzua, Oscar: Abdominal Wound Penetrating Gravid Uterus Injuring Fetus. Pregnancy Uninterrupted, Bol. Soc. chilena de obst. y ginec. 55: 417, 1939.

A 32-year-old woman seven months pregnant was hospitalized. She was suffering with multiple knife wounds, through one of which, below the umbilicus, omentum and several loops of intestine protruded. At laparotomy a gravid uterus was found, having a linear 2 cm. wound in the fundus. As no blood or amniotic fluid appeared, the laceration was closed in two layers. Recovery was uneventful and the patient was discharged in nine days, experiencing a small intermittent discharge of small quantities of fluid per vaginam. Two months later she was spontaneously delivered of a live 1,560 Gm. baby. The infant was cyanotic and dehydrated. On the superior and lateral aspects of the left thigh, there was a 2 cm. linear wound, clean and open, covered by a thin transparent pellicle, showing no tendency to cicatrization. The infant died in six days, and on post-mortem examination, a hematoma was found beneath the wound, infiltrating the thigh and extending to the gluteal and lumbar regions. The author discusses the indications for laparotomy in emergencies during pregnancy.

R. J. WEISSMAN.

Thomson, A. M. Wright: Post-Partum Retinal Arterial Obstruction Associated With Hemiplegia, Brit. M. J. 1: 387, 1940.

The author reports a case of retinal arterial obstruction accompanied by contralateral hemiplegia following the termination of pregnancy. The eye was permanently damaged but the hemiplegia disappeared rather rapidly. The writer suggests

Giuffrida, Francesco: **Fibromyomas and the Puerperal State**, *Rassegna d'ostet. e ginec.* 49: 18, 1940.

The author reports 11 cases of fibromyomas in gravid women occurring under his observation.

Four of the 11 patients were subjected to myomectomies while pregnant from two to three months. Two of these patients aborted the next day, one terminated with normal delivery, but proluton was used postoperatively to prevent abortion; the fourth patient was delivered vaginally at term, but the labor was complicated by placenta previa.

Four additional patients, pregnant forty days to six months, were treated by supravaginal or total hysterectomy. The three remaining patients were all delivered by laparotrachelotomy at term. Myomectomies were performed at the time of the sections.

The author concludes that with proper individualization of each case there is really little to fear from coexistent fibroids. Proluton is considered by him a valuable form of postoperative medication.

CLAIR E. FOLSOME.

Smalldon, J. L.: **Survey of Mental Illness Associated with Pregnancy and Childbirth**, *Am. J. Psychiat.* 97: 80, 1940.

The writer studied the records of 220 women admitted to the New York Hospital, Westchester Division, because of mental illness associated with childbirth and the puerperium. These cases comprised roughly 8 per cent of the female admissions during the period (1922 to 1938) under study. Manic-depressive psychoses accounted for 107 of the cases, dementia precox for 64, psychoneurosis for 28, psychosis with psychopathic personality for 10, toxic-exhaustive psychosis for eight, a psychopathic personality with pathologic emotionality but without psychosis for two and a paranoid condition for one. Only 3.6 per cent of the cases were classified as deliriums directly attributed to the toxic-exhaustive factors of reproduction, although such factors were frequently precipitating causes in the development of rather typical manic-depressive reactions, particularly of the depressive type. Probably this difference in diagnosis may be attributed to the increasing recent tendency away from the belief that a specific psychosis occurs in the pregnant and post-partum states and toward the conception that the physical and psychic problems of childbirth do not determine the type of psychosis but merely act as exciting or precipitating agents.

The study does not corroborate the fact that a high proportion of the depressive type of manic-depressive psychoses and puerperal schizophrenias are of paranoid reaction. It rather shows a greater percentage of catatonia. The study corroborates the observations of Strecker and Ebaugh that these schizophrenic reactions frequently show pronounced manic-depressive symptoms, clouding of the sensorium and a tendency to remissions, that these cases tend to slow deterioration and that a high percentage of post-partum psychoses occur in the Jewish race. The study tends to corroborate to some degree Zilboorg's claim that the aloof, shy woman with little previous contact with men and prolonged courtship tends to develop puerperal schizophrenia. Antagonism toward the child, as expected from Zilboorg's hypothesis, was present. With few exceptions the psychoses did have their onset post partum.

J. P. GREENHILL.

Miller, H. C. and Ross, R. A.: **Relation of Hypoglycemia to the Symptoms Observed in Infants of Diabetic Mothers**, *J. Pediat.* 15: 473, 1940.

The belief is widely held that the hypoglycemia of newborn infants whose mothers have diabetes mellitus is the cause of the cyanosis, muscular twitchings, convulsions, and, occasionally, the death of the infant. This assumption is naturally based upon the fact that hypoglycemia induced in older patients by the injection of insulin is accompanied by certain well-known symptoms which quickly disappear

This Board will hold its annual dinner for Diplomates, and others interested in the work of the Board, on Wednesday evening, June 4, 1941, at the Wade Park Manor Hotel, Cleveland, Ohio, immediately following the close of the Part II examinations. Diplomates certified at the preceding days' examinations will be introduced personally, and there will be several speakers.

Tickets at \$3.25 each may be obtained from Dr. Joseph L. Baer, chairman, 104 S. Michigan Avenue, Chicago, Illinois, or at the Registration Desk during the examination period.

Directory of Medical Specialists

A second edition of the Directory of Medical Specialists has been authorized by the Advisory Board for Medical Specialties, to be ready for distribution in February, 1942, with its contents complete to January first.

This Directory is the official publication of the Advisory Board, and will list the names of approximately 18,000 diplomates of the fifteen American Boards examining candidates for certification in the specialties. This is an increase of 4,000 over the first edition issued early in 1940.

The geographic grouping will give completely revised biographic data about each diplomate; there is an alphabetic index with addresses and specialty designations; and the plan of organization, officers, and examination requirements of each American Board are fully outlined in their various sections.

The biographic data of diplomates will not only be revised to date, but also will include much new information not found in the first edition. Details of formal training is one of these, and military appointments now held is another.

Only those who have been formally certified by one of the American Boards can have their names included, and all of these are included, there being no charge or obligation other than certification for such listings.

The official nature of this Directory makes it invaluable as a reference book. It may be used generally for the referring of patients to distant communities; for the information of Medical Society officers; for gaining detailed knowledge about qualified specialists throughout the United States and Canada; for the obtaining of detailed information about the American Boards; and for many other purposes.

The first edition had a wide distribution not only throughout the medical profession as well as medical and other public libraries, but also among insurance companies and business firms dealing with physicians. Nevertheless, it is not a commercial undertaking as the Directory contains no advertising material, is underwritten by the Advisory Board and actually received subsidizing support so that it could be distributed as near to cost as possible.

Questionnaires for biographic data are now being mailed out with order forms. The Secretary of each Board urges that every diplomate return his questionnaire form as quickly as possible, and he is urged also to support this project of the American Boards by his subscription to the Directory. A substantially reduced rate is offered for prepublication orders, as the size of the printing is based largely on advance subscriptions.

The publication is issued through the Columbia University Press of New York. The Secretary of each American Board serves on the Advisory Editorial Board, and Paul Titus, M.D., 1015 Highland Building, Pittsburgh, Pennsylvania, of the American Board of Obstetrics and Gynecology, is the Directing Editor.

that thrombosis of the pituitary artery with protrusion of the clot into the lumen of the internal carotid artery occurred. The collapse occurring after delivery slowed circulation and allowed a fresh clot to form in the ophthalmic and the middle cerebral artery. The clot in the middle cerebral artery was probably not complete and permitted the disappearance of the hemiplegia.

FRED L. ADAIR AND GEORGE BOHLENDER.

Pearce, T. Vibert: *Childbirth After Presacral Neurectomy*, Brit. M. J. 1: 87, 1940.

The literature on pregnancy following presacral neurectomy is reviewed briefly, and the author presents a case of his own. He concludes that this operation has no deleterious influences on pregnancy and labor and that in a small proportion of the cases the first stage of labor is rendered painless and rapid.

FRED L. ADAIR AND GEORGE BOHLENDER.

Russ, Witten B.: *The Maintenance of Pregnancy in the Human After the Removal of Both Ovaries*, Ann. Surg. 111: 871, 1940.

The author reports a case in which pregnancy continued after bilateral oophorectomy. The patient was a multipara who developed a torsion of the left adnexa in her second month of gestation. The right adnexa had been removed previously. The patient was given 1 c.c. of progesterin on the second postoperative day, and this was continued every other day up to the end of the fourth month. The patient was delivered of a normal, eight-pound, male child. The case is reported as interesting chiefly because of the general impression that abortion is almost certain to result from the loss of both ovaries during pregnancy, especially during the first three months.

WILLIAM BERMAN.

Sadowsky, A.: *Twin Pregnancy (A Discourse on Pathology)*, Monatschr. f. Geburtsh. u. Gynäk. 110: 81, 1940.

At the Hadassah-Rothschild Hospital (Jerusalem) in a series of 11,214 deliveries, Sadowsky found 161 twin pregnancies. Analysis of these cases showed that in twin pregnancies there is a greater tendency to toxemias, especially eclampsia, an increased incidence of abortions and premature labors, a higher percentage of operative deliveries, an increased maternal morbidity, a greater number of intra-uterine fetal deaths, and a higher infant mortality during the first week of life.

J. P. GREENHILL.

Items

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Cleveland, Ohio, by the entire Board from Wednesday, May 28, to Monday, June 2, 1941, inclusive, prior to the opening of the annual meeting of the American Medical Association in Cleveland.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

It is our intention to review all the reported cases, to discuss the pathogenesis, and to emphasize further the conclusive nature of the evidence by presenting cases of our own.

In the treatment of advanced cancer, we must realize the true limitations and be content with palliation rather than intensive therapy, the consequences of which might be worse than the original disease. Only the tyro will rush up with radiologic heavy artillery in a last-minute attempt to save a patient already doomed by advanced malignancy. But, since early cancer, if neglected, inevitably leads to death, only prompt and radical therapy may avert a fatal outcome. Even here,

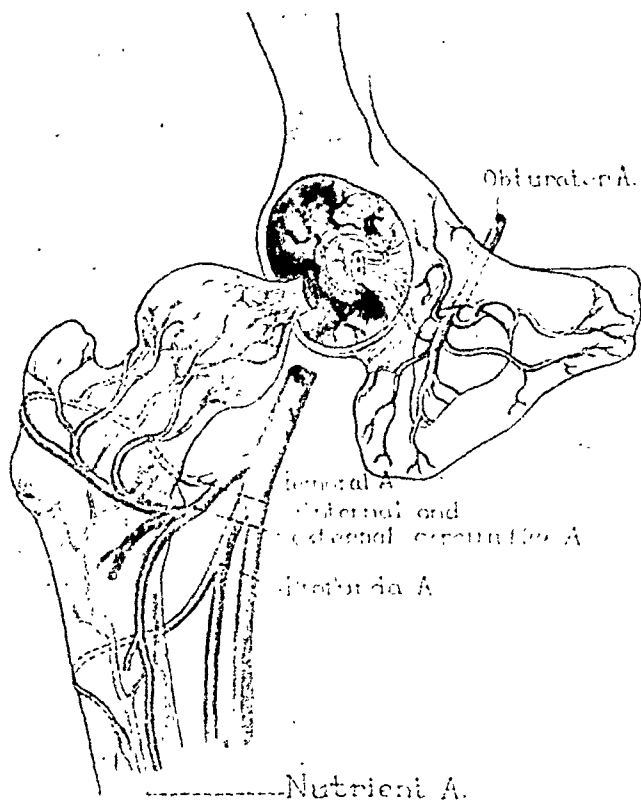


Fig. 1.—Schematic illustration of the blood supply of the head and neck of the femur.

however, enthusiastically intensive therapy may lead to sequelae which are often serious and occasionally calamitous and certainly fracture of the femoral neck is one of these. Since the use of lateral ports increases the incidence of fracture, we must ask whether the so-achieved slight increment in depth dose justifies their use.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

As noted by Kolodny,² the subject of femoral neck fractures is still obscure even to orthopedists; to gynecologists it is almost alien. Indeed, only since the advent of high voltage therapy has the subject assumed any gynecologic significance. The blood supply to the femoral neck, comparatively poor at best, is derived from the vessels of the periosteum, diaphysis, and ligamentum teres. With advancing age, the last named diminishes in importance.

American Journal of Obstetrics and Gynecology

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JUNE, 1941

No. 6

Original Communications

FRACTURE OF THE FEMORAL NECK FOLLOWING ROENTGEN THERAPY FOR GYNECOLOGIC MALIGNANCY

HYMAN STRAUSS, M.D., AND JOSEPH L. MCGOLDRICK, M.D.,
BROOKLYN, N. Y.

*(From the Gynecological Service of the Brooklyn Cancer Institute, Division of Cancer,
Department of Hospitals)*

OCCURRENCE of fracture of the neck of the femur as a sequel to radiation therapy for gynecologic malignancy is a serious complication. Excluding pathologic fracture due to metastases, the evidence is becoming more conclusive that some fractures may be directly attributed to the radiation effects on the normal bone and its vascular supply. Indeed when we consider that in irradiating pelvic malignancies the bony structures must necessarily be exposed, it is surprising that more complications are not noted. In some techniques, notably when true lateral trochanteric portals are used to attack the neoplasm, the femoral necks and their blood vessels receive an unusually large amount of direct radiation in addition to backscatter from other portals. More emphasis must be placed on the possibility of fracture as a sequel to such exposure.

Adult bone has always been considered as relatively resistant to radiation. This is a relative statement which should not be interpreted as meaning that adult bone is wholly immune to such effects. If enough radiation is given, the vascular, periosteal and bone changes will inevitably be such as to result in serious complications.

The literature confirmed our own findings of fracture of the femoral neck as a complication of irradiation for pelvic malignancies. However, this appeared for the first time in American literature in 1936.¹

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

and especially the epiphyseal vessels and very little upon those vessels in the ligamentum teres. He concludes his study as follows: "The question of healing of fractures of neck is entirely dominated by the difference of nutritional conditions in different types of fractures and in various ages of the patient." The present paper is, of course, concerned only with adult bone. A personal communication from A. F. Sava, based on a number of anatomic dissections, states: "The circulation of the femur proximal to the intertrochanteric line is supplied via capsular vessels . . . circumflex branches of the femoral. These form a complete ring about the femur (at the intertrochanteric line) and from this vascular ring branches run upward to supply the surgical neck and the head of the femur. I see no way in which these very important vessels could escape being in the line of fire in deep therapy of the pelvic structures, particularly through a lateral port."

NONRADIATION CAUSES OF SPONTANEOUS FRACTURE

Nutritional Defects.—Another factor which concerns the study of fractures is nutrition. Impaired diet resulting in basic nutritional deficiencies such as demineralization due to the disturbed calcium-phosphorus-vitamin D relationship has long been known in pediatrics. The study of adult nutrition unfortunately has not kept pace with that of the child. A recent editorial¹¹ has stressed the importance of gradual demineralization, affecting not only the skeleton, but the kidneys and other vital organs as well. Maxwell¹² has shown that acute calcium-vitamin D starvation in the adult is the etiologic factor in osteoporosis. The generalized form of osteoporosis may be a gradual and asymptomatic form of osteomalacia. Bernheim¹³ has demonstrated that, with senescence, the ability of the intestinal tract to absorb mineral salts decreases. Other investigators have linked the gradual decrease of hydrochloric acid content in gastric secretions of older persons with diminished calcium absorption, resulting in possible osteoporosis. With the exception of the parathyroid and the ovary, the relationship of the other endocrines to this disturbance is not sufficiently established. Recent experimenters are administering estrogens in the treatment of fractures.

Metastases.—The most frequent cause of spontaneous fracture seen by the oncologist is that due to metastases. However, in 1900 (before radiation therapy could affect the statistics), Cullen¹⁴ stated: "The patient usually dies before there has been sufficient time for extension to the bones to take place. Some cases, however, have been observed." Bone metastasis from cervix carcinoma is of such rarity that it is the subject of a forthcoming paper.

Taylor¹⁵ and others have emphasized the value of radiation castration in mammary cancer. This is predicated on the basis of a hormonal relationship. If a castration dose (in breast cancer) is sufficient to combat or prevent bone metastases, should not a relatively much larger dose given for a pelvic malignancy be even more efficacious in inhibiting bone metastases? May this not be the reason why bone metastasis from cervical malignancy is so rare when treated radiologically?

RADIATION THERAPY

The etiology, prophylaxis, and treatment of bone injury have become even more complicated with the advent of higher roentgen dosages by the single massive or the prolonged continuous techniques. Until recently adult bone had been considered relatively immune to radiation. As late as 1928, Groedel and Lossen¹⁶⁻¹⁸ in their encyclopedic volumes on *Roentgen Accidents and Injuries, etc.*, fail to mention spontaneous fractures of the femoral neck as a possibility. This we regard as highly significant. In 1930, Flaskamp in his monograph, *Damages Through X-rays and Radioactive Substances*¹⁹ says, "The healthy bone of the adult appears to be very radio-resistant." Even in 1934, Colwell and Russ²⁰ say: "Adult bone is relatively resistant to x-ray and injuries from this cause are rare. . . . We are unaware of any bone lesions reported from this cause." They further state that out of hundreds of cases of mammary cancer irradiated they had never seen injury to bone or cartilage. However, in a recent personal communication, Pack mentioned five cases of rib fracture following radiation therapy for mammary cancer. Colwell and Russ, nevertheless, do remind us that the unprotected hands and wrists of the pioneers did develop undue fragility and de-

The anatomy of these parts can best be described by quoting Gray:³ "The acetabular branch (of the medial femoral circumflex artery) arises opposite the acetabular notch and enters the hip joint beneath the transverse ligament in company with an articular branch from the obturator artery; it supplies the fat in the bottom of the acetabulum, and is continued along the round ligament to the head of the femur." Elsewhere, Gray⁴ says: "The nutrient artery of the femur is usually given off from the second perforating artery; when two nutrient arteries exist, they usually spring from the first and third perforating vessels." He⁵ further states: "The anterior surface of the neck (of the femur) is perforated by numerous vascular foramina." Spalteholz⁶ also demonstrated vascular foramina along the linea intertrochanterica.

Lippman and Zemansky⁷ have shown that, in animals, the vessels of the round ligament are essential for the normal development of the femoral head until maturity and that interference with the circulation results in deformity. After

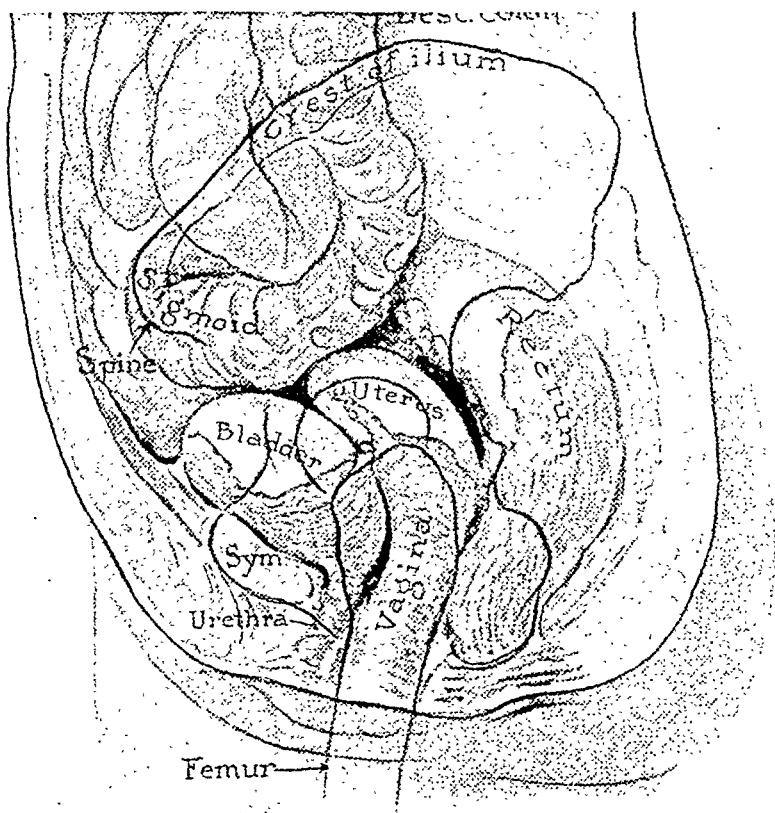


Fig. 2.—Femoral outline superimposed over pelvic viscera. (Permission of S. H. Camp Co.)

adolescence when the epiphysis has united with the shaft the importance of these vessels diminishes, they no longer carry blood into the femur and nutrition of the head is derived entirely from below. They assume that the same changes occur in the human being. The round ligament arteries are functionally end arteries and though capillary anastomoses between them and the peripheral epiphyseal branches do occur; experiments have shown that they are insufficient to preserve the viability of the affected part. Lippman,⁸ in another study in which he quotes Bergman, mentions the significance of the occlusion of the lateral epiphyseal vessels in producing pathologic changes. Since Albee⁹ finds that it is necessary to conduct blood to the anemic capital fragment in his treatment of femoral fractures, may we not infer that vascular disturbances may be an etiologic factor?

Kolodny¹⁰ states that the nutrition of the femoral head and neck in advanced middle life depends upon the diaphyseal end branches, the periosteal blood vessels,

TABLE I. SUMMARY OF REPORTED CASES OF FRACTURE OF NECK OF FEMUR FOLLOWING RADIATION

AUTHOR	AGE OF PT.	CARCINOMA OF	RADIUM MG. IIR. OR MC. IIR.	NO. OF CASES	ROENTGEN THERAPY DOSAGE PER PORT	PORTALS		A	P	INTERVAL BETWEEN THERAPY AND FRACTURE	FRACTURE ONE OR BOTH	COMMENT
						2 LATERAL	OBLIQUE					
Baensch, 1927	45	Cervix	7244	1	2 sed	+		+	+	3 yr.	Both	
Baensch, 1932	62	Ovary	None	1	?	+		+	+	1½ yr.	Right	Autopsy
Phillip, 1932	62	Cervix	Moderate dose	1	Large dose	+		+	+	Soon	Both	
Phillip, 1932	68	Cervix	6864	1	2 sed	+		+	+	2 yr. 2 mos.	Right Left	
Phillip, 1932	55	Cervix	None	1	2 sed	+		+	+	2 yr.	Right	Schauta operation before
Phillip, 1932	68	Cervix	5088	1	Over 2½ sed	+		+	+	1 yr.	Left	
Kropp, 1934	67	Cervix	1836 to vault	1	?	0	1 vulva port	+	++	3¼ yr.	Left	Wertheim operation before
Baclesse and Regaud*				3	?							
Dalby, Jacox, Miller, 1936	42	Cervix	5000-6000	14 cases 3 of whom received radium	1500-2000 r.	0	2 posterior oblique	+	+	19 mo.	3 Bi-lateral	17,280 r. total 1 autopsy 1 open operation 11,840 r. total
Dalby, Jacox, Miller, 1936	78		Tandem and Bomb		Series repeated 2-3 times at intervals of 3-6 months					3 yr. average	11 Uni-lateral	
Dalby, Jacox, Miller, 1936										73 mo.		

creased bone density. They attributed this to vascular changes impairing bone nutrition, which were prominent in such cases.

On the other hand, as far back as 1922, Regaud²¹ noted bone necrosis following x-ray or gamma radiation. He thought that the calcium and phosphorus of the bone set up secondary radiations of a more caustic nature which caused damage to the vital parts of the osseous tissue. This action may remain latent until some determining cause stirs it into activity, e.g., trauma or microbial infection. Even earlier, in 1910, Cluzet²² had demonstrated that radiation inhibits or delays the formation of callus after fractures; this is probably due to the devitalized osteoblasts in the periosteum which prevent bone regeneration. Recamier²³ demonstrated experimentally that bone growth could be retarded by a roentgen dose so small that it effected no change in the skin or histologically demonstrable changes in the bone cells. Ewing²⁴ states that the periosteum of all bony structures is most susceptible to irradiation. Regaud²⁵ says: "The irradiated bone burns and burns the periosteum and mucosa enveloping it."

The subject of osteoradionecrosis is thoroughly covered by Watson and Scarborough,²⁶ who attribute its development to irradiation, trauma, and then infection. Roentgenograms are of little value in the early stages of this disease. Late osteoradionecrosis has been observed by them eight and one-half years after successful treatment. According to them, "Syphilis is definitely not a factor in the etiology." They warn us: "It has been recognized that the responsibility for the serious complication of osteoradionecrosis rests entirely with the physician who outlines and carries out the irradiation measures, just as the surgeon must assume the major responsibility for an operative death."

SURVEY OF CASES REPORTED

The literature shows Baensch²⁷ to be the first to have reported a case of osseous injury following gynecologic irradiation. However, in his report in 1927 he credits Perthes and Jungling with having previously reported bone necrosis in connection with a roentgen ulcer. He also mentions Rahm observing mandible necrosis without preceding ulcer. In 1932 Baensch²⁸ reported a second case and concluded, "Without doubt the spontaneous fractures described above were attributed to the effect of irradiation because no other condition responsible for a pathologic fracture could be found."

Philipp,^{29, 30} in 1932, reported four cases of postradiation fracture in which no skin breakdown occurred. He states that he had never seen a spontaneous fracture unless the patients had received therapy from lateral ports. All of his patients received large but not excessively large doses. He concluded: "In forensic respects these cases are of importance in so far as one cannot infer an overdosage from the development of a fracture."

Kropp,³¹ in 1934, also reported a case. Baclesse³² and Regaud have observed three cases. We quote a personal communication: "We have observed three cases of such a fracture. In two cases there was evidently no metastasis because patients were living more than five years after x-ray application. In the third case, the radiographical findings were not so evident; the patient, treated four years ago, is still alive and suffering from her fracture, which is not actually healed. Is there a metastasis? We are following the patient." It is very likely that radiation therapy might have modified the osseous structures of the femoral neck to such an extent that "however insignificant a trauma might have produced a fracture."

The first American cases of this condition were reported by Dalby, Jacox, and Miller¹ in 1936. They cited 14 histologically demonstrated pelvic malignancies. In no instance was neoplastic growth demonstrated roentgenographically at the fracture site.

The radium was given via tandem tubes in the uterus and a bomb application against the cervix for an average dose of 5,000 to 6,000 mg. hr. They emphasize that "radium, as generally employed, probably has little effect on the femoral neck." Furthermore three of their patients received no radium at all. The x-ray therapy factors were 200 KVP, 0.5 mm. Cu. through four portals of 10 by 15 cm. in size, applied over two anterior and two posterior oblique fields. No lateral

trochanteric ports were used. Each series consisted of approximately 200 r. (measured in air) applied to each port every second to fourth day until a total of 1,500 to 2,000 r. was reached. The series were repeated two or three times at intervals of three to six months. In 6 patients the skin over the treated area was found in perfect condition. Two showed considerable telangiectasia, 6 showed bronzing and none showed serious skin damage or ulceration. An average period of three years (shortest 19 months, longest 73 months) intervened between the diagnosis of malignancy and fracture. The fractures were bilateral in 3 cases, occurring at intervals of ten, thirteen, and fourteen months, respectively. In no case was there a history of trauma. However, every patient complained of pain starting in the hip and radiating down the anterior thigh to the knee, for an average of seven months before the fracture was demonstrated. Pain on motion or weight bearing was also noted. However, the typical radiating pain described above may be due to ureteral stenosis.³³

There were only two histologic studies of the fractured structures, one a result of an open operation and the other an autopsy following death from an injury. In addition to radium, these patients received 17,280 r. and 11,840 r., respectively.

"The incidence of fracture of the femoral neck in this series is definitely higher than in a comparable group of the general population."³⁴ "An incidence of 2.1 per cent appears to be more than incidental."

In 1938, Miller and Folsome³⁵ mention 21 additional proved cases of spontaneous hip fractures in their clinic since the report in 1936. This brings their total number up to 35 cases.

Healy and Frazell,³⁶ in 1937, reported two such cases in over 3,000 pelvic malignancies irradiated.

Kalayjian,³⁷ in 1938, reported a case of bilateral fracture of the femoral neck.

In the course of discussion at the American Radium Society Meeting at San Francisco, June, 1938,³⁸ the following additional cases were reported: Costolow of the University of Southern California, 1 case (over 1,200 carcinomas of the uterus treated); Henry Schmitz of Chicago, 1 case (in over 1,000 cervical carcinomas treated); Zoe A. Johnston of Pittsburgh, 1 case.

In a subsequent personal communication, Dr. Z. A. Johnston mentioned that she had seen another case.

Robert G. Douglas of the New York Hospital has seen two cases. Clara Okrainetz³⁹ of Montefiore Hospital, New York City, reported a case in 1939.

In order to determine if there were other nonreported cases, a questionnaire was sent out. Those reporting in the affirmative (published and unpublished) have been detailed above. To show the rarity of this condition, note that the following have not observed any cases:

B. F. Schreiner, State Institute for Malignant Diseases, Buffalo
 Edw. F. Skinner, St. Luke's, St. Mary's, Kansas City General
 A. E. Hayward Pinch, London Radium Institute
 Curtis F. Burnam, Howard Kelly Hospital, Baltimore
 Francis C. Wood, Crocker Institute & St. Luke's Hospital, New York City
 Lawrence A. Pomeroy, Cleveland City and Lakeside Hospital
 A. N. Arneson, Washington Univ. Med. School, St. Louis, Mo.
 U. V. Portmann, Cleveland Clinic
 Geo. E. Pfahler, University of Pennsylvania, Philadelphia
 Geo. G. Ward, Woman's Hospital, New York City
 A. U. Desjardins, Mayo Clinic
 Charles L. Martin, Baylor University
 Maurice Lenz, Columbia-Presbyterian, N. Y., Med. Center
 Charles A. Walters, Johns Hopkins Hospital
 Rollin H. Stevens, Grace Hospital, Detroit
 H. B. Hunt, Univ. Neb., Neb. M. E. Hospital, Douglas Co. Hospital
 H. H. James, Murray Hospital, Butte, Mont.
 James Heyman, Radium Hemmet, Stockholm

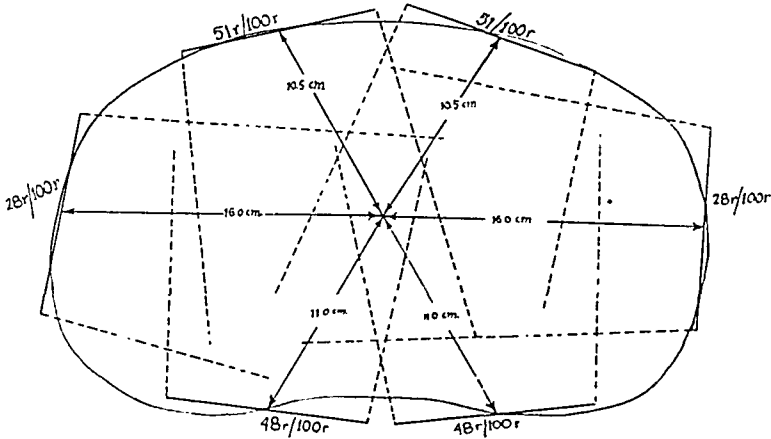
Dr. U. V. Portmann made the following comment: "It is quite likely that the bone changes are produced by irradiation of lateral fields to the pelvis, which I

Miller and Folsome, 1938				21 cases additional	Same technique			2 posterior oblique	+	+				
Healy and Frazell, 1937	57	Cervix stump	3009 MCH	1	750 r. repeated				+	+		4½ yr.	Right	
Healy and Frazell, 1937	56	Cervix	3000 MCH	1	1800 r. 1500 r.	+			+	+		2¼ yr.	Left	
Kalayjian*	68	Cervix	3000	1	1500 r.	0			+	+		9 months	Both	
Costolow				1										1 case in over 1200 cervix cancers
Henry Schmitz*				1										1 case in over 1000 cervix cancers
Zoe A. Johnston*				2										
Robert G. Douglas*				2										
Clara Okrainetz		Ovary		1		Rt. +								

*Personal communication.

vaginal vault, freely movable and no parametrial infiltration. X-rays at this time showed no evidence of pulmonary or osseous metastases. Phenolsulphonephthalein test normal. Pyeloureterogram negative.

Under cyclopropane anesthesia, 6 radium needles were inserted into the cervix and a colpostat into the fornices. Factors: Six 2 mg. radium element needles, 35 mm. long, $\frac{1}{2}$ mm. Pt. filter = 12 mg. Two 20 mg. radium element tubes in a colpostat, 1.0 mm. Pt. filter = 40 mg.; duration, 74 hours; dosage, 3,848 mg. hr.



R_c
SIX PORTS TO PELVIS.
TWO ANTERIOR LATERAL
& POSTERIOR SIZE 10.15 cm
2Cu 1A1, 50 cm S.T.D. 200KV
200r TO THREE PORTS DAILY
FOR TOTAL OF 3000r TO
EACH

TUMOR DOSE
RT. ANT. 51.30 1530
LT 1530
RT LAT. 28.30 840
LT 840
RT POST. 48.30 1440
LT 1440
Total r 7620

Fig. 3.—Case 1. X-ray therapy factors and dosage.



Fig. 4.—Case 1. Radiation reaction outlining right lateral port.

Two weeks later a uterine tandem was introduced after dilatation of the cervical canal. Factors: A tandem of three 10 mg. tubes of radium element (30 mg.), 1 mm. of Pt. filter; duration, 50 hours; dosage, 1,500 mg. hr.

Five months after starting roentgen therapy she first complained of pain in right thigh radiating down to the knee.

never use." Dr. Chas. L. Martin wrote: "Never used lateral ports and our technics have never been of the excessively severe type." May not the absence of cases in the above clinics be due to the technique and dosage?

PERSONAL OBSERVATIONS

CASE 1.—Mrs. L. S., a 37-year-old Jewess, was admitted to the Brooklyn Cancer Institute Jan. 5, 1938, with the complaint of profuse postcoital bleeding of ten days' duration.

Family and Past History irrelevant except menopause at the age of 26, when both ovaries were removed because of some obscure post-partum complication.

Present Illness.—Five months ago she noticed a scant whitish, watery, nonblood-tinged leucorrhea. Ten days before admission, following coitus, she noted profuse vaginal bleeding which has persisted.

Admission examination was negative except for the vaginal examination which showed a mobile cervix, high in vaginal vault with no parametrial infiltration or thickening. The anterior lip was smooth and regular. The posterior lip had a small proliferative nodular growth, no larger than the "tip of the finger," which bled on manipulation. Corpus and adnexa were negative. Rectal examination confirmed the vaginal. Impression: "If this is a carcinoma of the cervix, it is a Schmitz No. 1 and amenable to treatment."

Laboratory reports were entirely negative except the *biopsy* which showed transitional cell carcinoma of the cervix.

Complete pelvic cycle of roentgen therapy was given between January 11 and April 1, 1938 (38 treatment days), using the following factors: 6 ports to the pelvis, 10 by 15 cm. each, 2 anterior, 2 lateral, 2 posterior, rotating right and left side daily; 200 r. units to each port for a total of 3,000 r. units measured in air, without backscattering; 200 kv.; 20 Ma., 2 mm. Cu., 1 mm. Al., filtration; 50 cm. S.T.D. She received 15 treatments to each port, cross-firing the pelvis as indicated. For each 100 r. given at skin without backscattering the different depths received doses shown in Table II.

TABLE II

DEPTH	100 R.	AT SURFACE WITHOUT BACKSCATTER	3000 R. TOTAL PER PORT
0 cm.	136 r.		4080 r.
1 cm.	140 r.		4200 r.
2	133		3990
3	120		3600
4	109		3270
5	98		2940
6	88		2640
7	78		2340
8	69		2070
9	61		1830
10	54		1620
11	48		1440
12	42		1260
13	38		1140
14	34		1020
15	31		930
16	28		840
17	25		750
18	22		660

Tumor dose is approximately 7,620 r. units. The tumor dose, without lateral ports, would have been 5,940 r. units. For each 100 r. units at the surface each anterior port contributed 51 r., the posterior 48 r. and the lateral 28 r.

One week after completing therapy, patient was admitted to hospital for insertion of radium. Vaginal examination showed cervix to be smooth, firm, flush with the

radiation changes in the skin over the radiated ports were noted. X-rays at this time "did not show bony callus." Sandbags were used for immobilization.

Jan. 10, 1939, one year after the initial visit, a careful check-up showed that her phenolsulphonephthalein test was now 31 per cent in two hours and a marked bilateral hydronephrosis and hydroureter had developed. A rectovaginal fistula was found. Vesicovaginal fistula was suspected, but never proved because of her general condition. She developed pain in her left hip which gradually became more severe; repeated roentgenograms failed to show osseous changes which might precede a fracture. Clinically and roentgenographically she showed signs of intestinal obstruction. She died Jan. 29, 1939, one year and twenty-four days after her initial visit.

Autopsy report by Dr. Herman Bolker, Pathologist. The following are the essential findings on post-mortem study. Several loops of ileum were bound in the pelvis and intimately adherent to one another. They were kinked upon themselves at several points, and in one loop there was an irregular, punched out, ulcerated area with a necrotic base roughly 2 cm. in diameter, which extended in the gross into the muscularis; no evidence of it was seen on the serosal surface. From a point 6 cm. proximal to the anal orifice, the rectal wall was surrounded by a very dense, fibrous tissue, which extended upward for a distance of 10 cm. The muscularis was well defined in this area, but the mucosal folds were flattened, and a large fistula to the vagina measuring 2.5 cm. in diameter was found at a distance of 8 cm. from the anus. The edges were smooth and rolled. There were two other fistulas, both in the anterior wall, one 2 cm. below, and the other 3 cm. above the large fistula. Each of these was 1 cm. in diameter. The only recognizable portion of uterus which remained was a small mass of firm tissue, found in the expected anatomic position of the organ. The urinary bladder was contracted, and thick-walled. Its wall was grayish green in appearance, and resembled that of the vagina, which was also gangrenous. There was considerable periureteral dense fibrous tissue in the parametrial areas. The ureters were not grossly dilated; they could be traced without difficulty to the renal pelves. The calyces and pelvis on the left were slightly dilated.

There were several rectangular brown discolorations of the skin over the upper femoral, sacral, and inguinal regions, bilaterally corresponding to the ports used in the radiation therapy.

The upper third of the right femur was removed, and a distinct coxa vara was noted. On section there was evidence of a healed fracture at the neck corresponding with the roughened area at the inferior edge of the neck externally. The cortex in this area appeared thickened, while the remainder of the cortex about the head was rather thin. The marrow of the head and trochanteric region was yellowish and showed no areas of neoplastic involvement. It was somewhat more dense in the line across the neck. The marrow of the shaft was soft and yellowish red.

The other pertinent findings were vesicovaginal and rectovaginal fistulas, marked parametrial fibrosis and several punched out ulcers in the small intestine, judged due to radiation.

The immediate cause of death was pneumonia.

Microscopic findings were as follows:

Uterus.—The greatest portion of the lining was replaced by a necrotic and purulent layer. Much of the wall had undergone complete coagulation necrosis. Several areas, however, were invaded by sheets of atypical squamous cells, which occurred in discreet groups, and showed central necrosis, lysis, or keratinization. The individual cells had poorly defined cell boundaries, a deep pink cytoplasm, and vesicular or hyperchromatic nuclei, which varied considerably in size and shape. Inter-cellular bridges were not demonstrable. There were no mitotic figures. Tumor cells were found in the parametrial fatty tissue. There was an infiltrate of moderate numbers of lymphocytes and plasma cells. Many of the large arteries showed considerable subintimal thickening.

Rectovaginal Fistula.—The tract was a necrotic and purulent one. The underlying tissue contained numerous masses of neoplastic cells similar to those found in the parametria. The vaginal mucosa had undergone coagulation necrosis. There was a scattered mono- and polymorphonuclear leucocytic infiltrate. Recent

Three months later she complained of pain in upper portion of right thigh and in an area lateral to the sciatic notch. Flexion of the hip with the knee extended yielded pain in above areas, also when walking upstairs or attempting to rise from a chair. No other pain was complained of.

X-rays of the pelvis and upper three-fourths of the right femur were negative.

Six weeks later (ten months after initial visit) rectal examination revealed indurated tissue encircling anterior half of the rectum about six inches from anus. Proctoscopy distal to the stenotic area showed many pin-point areas of hemorrhage on the anterior and right rectal wall. Biopsy from this area was nonmalignant.

On Oct. 20, 1938, a barium enema was given and reported as follows: "The barium enema flows in without difficulty until it reaches a point eight inches above the anus. Here, a slight delay takes place and the lumen of the sigmoid for a stretch of one inch is narrowed to one-half inch diameter and the outline is irregular. After evacuation the mucosal pattern in the constricted area was preserved.



Fig. 5.—Case 1. Fracture of right femoral neck. Stricture of large intestine. Barium enema after evacuation.

There is an intracapsular fracture of the right femur. The fracture line runs at right angles to the axis of the neck and is very straight. There is upward displacement of the distal fragment by about one-half inch. The bone does not show any visible pathologic changes. Conclusions: Organic constriction within the distal half of the sigmoid. Fracture of right femoral neck." The fracture was thus noted six months after completion of therapy and four months after onset of pain in the hip.

Blood chemistry, count, and sedimentation rate were normal. Wassermann and Kline tests were negative.

Blood calcium was 9.08 mg./100 c.c.; phosphorus, 4.63 mg./100 c.c.; phosphatase, 7.61 units.

A body spica plaster cast extending from the umbilicus down to the right ankle and to the left knee was applied.

Within a month of the application of the cast, the patient developed bronchopneumonia and severe pain beneath the cast, necessitating its removal. Extensive

dilated thin-walled vascular spaces. The adjacent cortex was undergoing resorption. Union between the fragments was entirely fibrous. The remaining trabeculae were small and undergoing decalcification. There was no evidence of new bone formation. The adjacent marrow was fatty; small areas of hematopoiesis were present. No neoplastic elements were found. The periosteum was thickened, particularly at the fracture site, and consisted of dense, poorly cellular, fibrous tissue. No osteoblasts were present. Many of the smaller arteries within the marrow and in the periosteal tissues had markedly thickened walls, with almost occluded lumina. The thickening was due almost entirely to widening of the sub-intimal layer. Inflammatory cellular infiltrate was scant and of the mononuclear variety. Sections through the head of the femur showed a covering of histologically normal hyaline cartilage. The cortex, marrow, and bony trabeculae showed no histologic changes. Sections through the ligamentum teres were composed of considerable dense, fibrous tissue. Several of the smaller arteries in the ligament showed marked subintimal thickening with the lumina narrowed to varying degrees, some being almost completely occluded. Vessels of the same size in the viscera showed no comparable thickening. The sections from the irradiated skin presented an atrophy of the epidermis with flattening of the rete pegs. The underlying corium shows considerable homogenation, and contains numerous chromatophores. There is a scant lymphocytic infiltrate, chiefly perivascular in location.

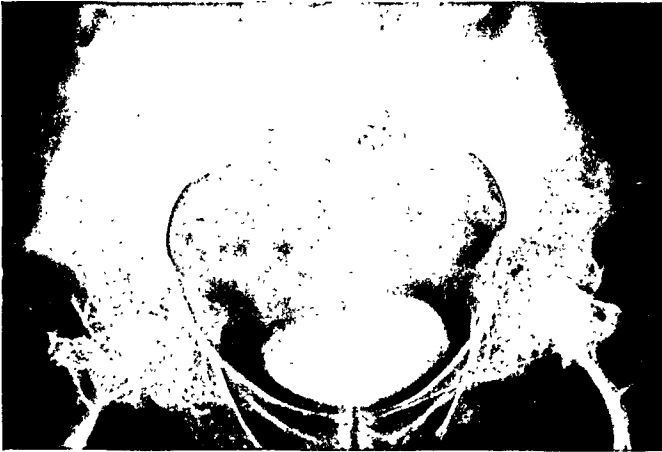


Fig. 8.—Case 2. Femoral heads moderately deformed, angulated upward. On the upper aspect of the right femoral neck, the cortex shows slight interruption of continuity. Intravenous pyelogram, cystogram, and ureterogram.

CASE 2.—Mrs. A. P., a 58-year-old Puerto Rican, para iii, was admitted Aug. 14, 1937, complaining of leucorrhea, weight loss, pelvic pain, and vaginal bleeding of 2 months' duration. Family and past history were irrelevant. Physical findings were mitral stenosis, secondary anemia, and a Schmitz III carcinoma of the cervix uteri. Vaginal examination revealed a firm, nodular, and fixed cervix with an ulcerated crater on its posterior lip, which on biopsy proved to be a squamous cell carcinoma. Parametria were bilaterally infiltrated. Uterus was slightly enlarged; adnexa, negative. Laboratory findings were essentially negative. Phenolsulphonephthalein excretion was low, in spite of negative cystoscopy and pyelography (retrograde and intravenous).

Roentgen therapy given from Aug. 17 to Sept. 25, 1937, consisted of the following factors:

200 kv., 50 cm. T.S.D., 2 mm. Cu. and 1 mm. Al filtration
Six ports (2 anterior, 2 posterior, and 2 lateral), 10 by 15 cm.
200 r. to each of 3 areas daily, rotating right and left, totaling 2,400 r. per port (or 14,400 r.), yielding a tumor dose of 6,814 r. units.

thrombi were present in the larger veins. The rectal mucosa showed considerable degenerative change. The mucosal and submucosal blood vessels were widely dilated. The pararectal tissue was a broad mass of fibrous tissue infiltrated with polymorphonuclear leucocytes.

Urinary Bladder.—The lining epithelium had desquamated. The mucosa was markedly edematous. There was considerable vascular dilatation. No neoplastic involvement was found in the vesical or ureteral walls.



Fig. 6.—Case 1. Section (autopsy) through fracture site in femoral neck with fibrosis avascularity.

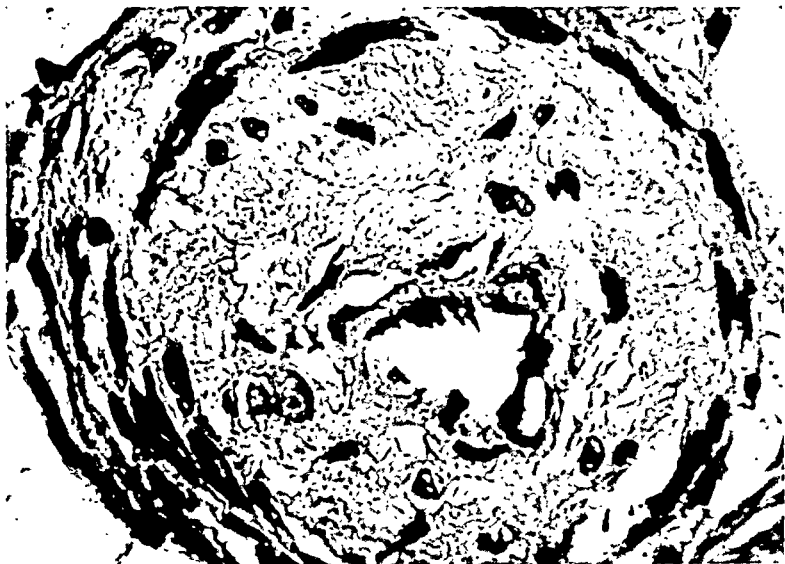


Fig. 7.—Case 1. Ligamentum teres with vascular lumen markedly narrowed.

Small Intestinal Ulcer.—The mucosa was completely necrotic, being recognized only by small suggestive plicae. The submucous fibrous tissue was greatly increased in amount and had replaced the muscularis in part. The ulcer at one point reached and involved the longitudinal layer of the muscularis. The fibrous tissue was infiltrated with moderate numbers of plasma cells, lymphocytes, and polymorphonuclears. The serosa was also markedly widened and had increased fibrous tissue.

Femur.—In sections through the fracture site, the cortex was absent over a wide area, being replaced by poorly cellular fibrous tissue. This contained numerous

Blood count was normal, serology negative for syphilis. Curettage of cervical canal showed a transitional cell carcinoma.

Radium was inserted on Aug. 10, 1938:

Uterine tandem 15 - 15 - 10 mg. radium	} 1½ mm. platinum filtration
Vaginal colpostat 15 - 15 mg. radium	
70 mg. for 92 hours = Dose 6,500 mg. hr.	

Roentgen therapy was given between Oct. 17, 1938, and Jan. 6, 1939, and consisted of the following factors:

200 kv., 50 cm. T.S.D., 2 mm. Cu. and 1 mm. Al filtration

Six ports (2 anterior, 2 posterior, and 2 lateral) 10 × 15 cm. in size
200 r. to each of 3 areas daily—alternating left and right for a total
of 2,400 r. each measured in air (total 14,400 r.), yielding a tumor
dose of approximately 6,204 r.



Fig. 10.—Case 4. Fracture of left femoral neck.

Following this, she gained weight, felt better, and had no complaints until six months later when she complained of pain in her chest. At this time x-ray of chest showed a small area in the right lung which was questionably metastatic.

Five months later, on Dec. 4, 1939, she complained of pain in the right upper thigh. Vaginal examination showed a frozen pelvis with infiltration to the lateral pelvic walls. X-rays of skull, spine, upper extremities, and legs were negative. X-rays of the femora and pelvis showed: "Intracapsular fracture of the right femoral neck with partial impaction and rarefaction in upper half. Sclerosis in the lower half of the fracture line." This was eleven months after completion of therapy. Blood count was normal at this time; blood calcium 9.52 mg. per cent, phosphorus 3.8 mg. per cent, phosphatase 8 units. A lateral splint was applied to immobilize the right femur. Subsequently at open operation, five Moore pins were inserted through the neck to the head of the femur. Healing was prompt. She is walking around with difficulty at present, and her general condition is only fair.

Sept. 27, 1937: Examination after completion of x-ray cycle showed marked regression in local lesion. Cervix was atrophied and flush with vaginal vault, and of normal consistency. Fornices were obliterated. Body of the uterus was atrophic. Parametrial thickening had practically disappeared.

Comment: "Excellent recession of local lesion, but constriction of vault and obliteration of fornices will definitely interfere with proper full radium dosage."

Radium therapy on Sept. 27, 1937, consisted of:

Uterine tandem of 10 and 10 mg.	} 1.5 mm. Pt. filtration
Vaginal corks of 10 and 10 mg.	
40 mg. \times 100 hours = 4,000 mg. hr.	

On Sept. 19, 1939, patient returned to the clinic, after an absence of two years, complaining of inability to abduct her thighs. Her weight was 95½ pounds. "Vaginal examination revealed an obliterated vagina which admitted one finger for a depth of 1½ inches. Cervix, uterus, and adnexa were palpable."

Intravenous pyelography showed both kidneys functioning well.



Fig. 9.—Case 3. Intracapsular fracture at junction of right femoral head and neck.

Roentgenographic report: "Bilaterally, the femoral head shows coarse trabeculation and a cherry-sized area of increased illumination surrounded by a ring-shaped shadow of increased density. The femoral head is moderately deformed (angulated upward). On the upper aspect of the right femoral neck, the cortex shows slight interruption of continuity. On the whole, the affection of both femoral heads is very symmetrical."

It was felt that the bone changes noted adequately explained her clinical symptoms. She has repeatedly refused to return to the hospital or even see the social worker.

CASE 3.—Mrs. A. D, a 64-year-old American housewife, para iv, was admitted Aug. 5, 1938, complaining of vaginal bleeding of three months' duration. Her family, past, and marital history were noncontributory, except for a fall five years earlier. Following this fall she promptly arose and walked home. She saw no physician, had no x-ray taken and suffered no disability except slight pain in right thigh with change in weather. Physical examination was irrelevant except for pelvic findings. Vaginal examination: vagina was moderately contracted; cervix, softened, small, smooth and not ulcerated, but there was a slight sanguineous ooze from the external os. Fundus was not enlarged. Bilateral parametrial thickening was present, more marked on the right.

TABLE III. SUMMARY OF AUTHORS' CASES

Factors used: Dosage calculated for portals in r. units (in air)
 6 portals—2 anterior, 2 posterior, and 2 lateral, 10 × 15 cm.
 200 kv., 20 Ma.
 Filtration 2 mm. Cu. + 1 mm. Al.
 T.S.D. 50 cm.

PATIENTS	FIRST L. S.	SECOND A. P.	THIRD A. D.	FOURTH M. F.
Age	35 yr.	58 yr.	64 yr.	64 yr.
Diagnosis	Cervix carcinoma	Cervix carcinoma	Cervix carcinoma	Cervix carcinoma
Schmitz Class	I	III or IV	III	III
Radium dose mg.hr.	5,348 mg.hr.	4,000 mg.hr.	6,500 mg.hr.	6,000 mg.hr.
Total r. units per port	3,000 r.	2,400 r.	2,400 r.	2,400 r.
Grand total	18,000 r.	14,400 r.	14,400 r.	14,400 r.
Tumor dose	7,620 r.	6,814 r.	6,204 r.	5,496 r.
Tumor dose without lateral ports	5,940 r.	5,206 r.	4,644 r.	4,224 r.
Interval between completion of therapy and diagnosis of fracture	6 mo. rt. femur	24 mo. bilateral	11 mo. rt. femur	20 mo. left femur
Treatment or operation	Body spica and sandbag immobilization	Refused	Operation, 5 Moore pins	Thomas splint or walking caliper
Progress	Autopsy	Barely able to walk	Walking with difficulty	Walking with difficulty

SUMMARY

We feel justified in presenting these cases as fractures of the femoral neck following radiation therapy of cervix carcinoma.

Repeated x-rays, particularly at the sites of fracture, were negative for metastases.

Frequent roentgenograms disclosed no osteitis fibrosa, destructive, neuropathic, or other recognizable bone disease entities.

It is generally conceded that syphilis is not an etiologic factor in this condition.

The incidence of femoral neck fracture in cases of gynecologic carcinoma treated by roentgen therapy is higher than that observed in a similar age group of the population.

Senescence certainly could not be an important factor in the first patient who was only 38 years old at the time of death.

Obesity can be ruled out etiologically, since the patients at most weighed between 96 and 140 pounds during the period of treatment.

Severe trauma is entirely excluded because the first patient was bed-ridden except for the necessary examinations and the others gave no such history. At no time did they complain of sudden sharp pain. The fracture was insidious and diagnosed fortuitously in the first case during a barium colon roentgenogram. Only one and one-half months previously the femur and pelvis were roentgenographically negative. In the other cases the diagnosis was made because of our previous experience.

Absence of bilaterality does not mitigate against the pathogenesis previously ascribed. If these patients live long enough, it is not improbable that more bilateral fractures will be observed. Our first case died within a year of the completion of her x-ray cycle. The remaining patients are still alive.

CASE 4.—Mrs. M. F., a 64-year-old Italian housewife, para xii, was admitted May 23, 1938. Cervical biopsy at another hospital showed squamous cell carcinoma, prickle-cell type. Menopause occurred at age of 41 years. For the past year she had a gradually increasing leucorrhea, and for the past month lower abdominal pain and swelling of the left leg. There was no bleeding.

Physical examination was essentially negative, except for pelvic examination which showed a slightly enlarged nodular fixed cervix with bilateral parametrial infiltration more marked on the right. X-ray films of the chest, spine, pelvis, and intravenous pyelography were negative, as were the electrocardiograms, blood count, chemistry, and Wassermann test.

Roentgen therapy consisting of the following factors was given between May 24, 1938, and July 1, 1938:

200 kv., 50 cm. T.S.D., 2 mm. Cu. and 1 mm. Al filtration
Six ports (2 anterior, 2 posterior, and 2 lateral) 10 × 15 cm.
200 r. to each of 3 areas daily, rotating right and left total-
ing 2,400 r. per port (or 14,400), yielding a tumor dose of
5,496 r. units.



Fig. 11.—Case 4. Fracture of left femoral neck, cone study.

Radium therapy was given on July 11, 1938. The factors were:

Uterine tandem 15 and 15 mg.	} 1.5 mm. Pt. filtration
Vaginal corks 15 and 15 mg.	
60 mg. × 100 hr. = 6,000 mg. hr.	

Pelvic examination at this time showed a markedly narrowed vagina, a cervix not palpable, and bilateral parametrial infiltration. The following month she developed a phlebitis of the left lower extremity which subsided under symptomatic therapy.

On April 1, 1940, she walked into the clinic with a noticeable limp and complained of pain in the left hip. This pain had been gradual in onset for the past four months. X-ray showed "intracapsular fracture through the upper end of the left femoral neck with $\frac{1}{2}$ inch upward displacement—and slight impaction of the fragments. No changes of bone structure can be detected."

She had less than 1 cm. shortening, with no appreciable eversion, and slight spasm on inversion. Pelvic findings were: occluded vagina and frozen pelvis. Treatment consisted of immobilization by sandbags, followed by a Thomas splint or walking caliper. She now walks with considerable difficulty.

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PREVENTION OF ASPHYXIA NEONATORUM*

A STUDY OF THE ETIOLOGIC FACTORS OBSERVED IN 2,000 CONSECUTIVE DELIVERIES

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PREVENTION of asphyxia neonatorum should be the acknowledged responsibility of every obstetrician as an integral part of prenatal care and the conduct of labor. There has been a tendency to accept asphyxia neonatorum as something unpreventable or at least unavoidable. Fatalistic acceptance of the latter view might seem justified upon superficial consideration of the fact that prematurity, trauma, and analgesics are ordinarily accepted as most important etiologic factors and that beyond a certain point these are truly unavoidable. This acceptance is confirmed in current literature concerning asphyxia neonatorum where the great majority of publications are concerned with treatment only.

The approach to this problem of prophylaxis should be similar to that of prevention of any disease as conducted along lines of preventive medicine in general. Before prevention can be instituted, a thorough

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Careful histologic examination of multiple sections from the fracture site and adjacent bone revealed no metastatic involvement.

In the case autopsied, since the right lateral trochanteric port received 3,000 r. units and the depth dose to the tumor through this port was 840 r. calculated at 16 cm. depth, the intervening tissue was of necessity irradiated. The skin showed marked bronzing and epithelial desquamation. Subcutaneous induration, ureteral occlusion, intestinal obstruction with stenosis and multiple fistulas were also present. All of these changes were bilateral. Due to the proximity of the femur to the surface, the depth dose to the bone and its vascular supply is practically the same as the surface dose. This must be borne in mind in evaluating the term "relative radiation resistance." Excessive dosage of roentgen therapy whether given in one prolonged cycle or in smaller repeated cycles imperceptibly reaches dangerous proportions whose consequences become more serious with the lapse of time.

The pathologic findings of the autopsy are characteristic of radiation effects.

CONCLUSIONS

This study was undertaken not with the intention of finding fault with the technique of the oncologic radiologist, but with the hope that we may profit, to the benefit of the patients, from a critical survey of the reported data of osseous radiation injury.

It is our conclusion that the small increase of depth dose via treatment through lateral ports does not justify the added risk. Also that doses of radiation even in prolonged, small, divided dosages, by their cumulative action, may produce serious injury even to a radiation-resistant structure-like bone. In repeating the cycle, the cumulative action must be carefully borne in mind.

Clarification of the pathogenesis is a necessary prerequisite for early correct diagnosis. Earlier diagnosis assumes greater importance as the incidence of the condition increases, which is to be expected as the percentage of ten-year survivals following roentgen therapy rises.

We must bear in mind that the vascular supply of the femoral neck is terminal and vulnerable to postradiation vascular occlusion. In most cases these patients are poorly nourished due to a calcium-phosphorus-vitamin imbalance. A critical evaluation of our own work requires us to revise our technique in the light of the above conclusions.

We cannot condemn all therapy which does not cure, since therapeutic nihilism, in a disease fraught with such dire consequences, is craven surrender. If we can do naught but alleviate the symptoms of advanced malignancy and make oncoming death more bearable, we are justified in using palliative therapy. However, we must keep in mind that we are treating the patient and not the disease.

We hereby express our thanks to Dr. S. Westing, Roentgenologist; Dr. H. Bolker, Pathologist; and Dr. M. R. Camiel.

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Various fundamental but somewhat isolated facts concerning the etiology of asphyxia neonatorum have appeared in the literature, most of them appearing in conjunction with discussions of pain relief.

The importance of excessive variations in fetal heart rate in relation to asphyxia was emphasized by von Winckels in 1893 and by others since that time. Knipe⁹ in his review of "twilight sleep" states that both Hocheisen and he found increased asphyxia following an increase in length of labor. Veit in 2,550 vertex labors reported 18.2 per cent asphyxia following two-hour second stage of labor and 49.6 per cent following a four-hour second stage. Shute and Davis¹⁰ more recently have described in detail the relation of morphine to the condition of the infant at birth. In addition to the effect of morphine itself, which caused 26 per cent narcosis, they found important such factors as time of administration, trauma of delivery, maternal toxemia, condition of the infant in utero, anesthesia and adjuvant sedatives. Lewis¹¹ concluded that a combination of any of several analgesic agents plus operative delivery greatly increased the incidence of asphyxia. Clifford and Irving⁷ observed less asphyxia with barbiturates than with opiates, and that the size of the dose and the time of administration of barbiturates was of no great significance. These later reports were the results of series of selected cases. The relation of trauma and prematurity were reviewed and summarized by Hess, Mohr, and Bartelme¹² who emphasized the relation of cyanosis to atelectasis and cerebral trauma. Clifford¹³ reported the relation of asphyxia to premature separation of the placenta.

Kosmak,¹⁴ in 1931, in discussing the viewpoint the obstetrician should take in asphyxia neonatorum, stated that it was something to be feared constantly and anticipated. He divided the causative factors as follows: (1) before delivery: pressure, prolapse and knots of the cord, placental separation, uterine tetany, narcosis, analgesia, and anesthesia. (2) During labor: trauma of forceps, pressure, and version. (3) During labor and delivery from sudden compression or release of the head passing through the birth canal. (4) Prematurity: with defective respiratory development. (5) Asphyxia from analgesics given the mother.

A similar classification by Moncrieff¹⁵ is as follows:

A. Central Factors

1. Immaturity of the center.
2. Damage of center: pressure, edema, hemorrhage, etc.
3. Narcotics.
4. Chemical factors: oxygen lack, carbon dioxide excess, etc.
5. Circulatory disturbances: cord pressure, etc.

B. Peripheral

1. Obstruction.
2. Delayed expansion.
3. Muscular feebleness.
4. Circulatory failure.

McGrath and Kuder¹⁶ studied 4,865 consecutive births in relation to asphyxia neonatorum, their primary interest being the peripheral factors involved. Mention was made that prophylaxis played an important part in reducing the effects of the central factors. They found that trauma increased asphyxia from 6.6 to 15.6 per cent and fetal mortality from 2.4 per cent to 10 per cent.

There has been considerable discussion in the literature about the correctness of the term "asphyxia neonatorum" and various substitutes have been suggested: apnea neonatorum, anarchapnea, respiratory failure, oligopnea, and others. While granting that the term "asphyxia neonatorum" is a misnomer, we feel certain that everyone knows the connotations that the words carry, and hence it will be used.

knowledge of the incidence, distribution, severity, and other modifying factors of the disease must be obtained. Some work has been done along these lines, and this report adds corroborative evidence, but more will be necessary before the various ramifications of this problem are completely understood.

Until recently, neonatal death has been considered the only serious consequence of asphyxia neonatorum. There can be no doubt about the high neonatal mortality following asphyxia, a fact repeatedly observed and reported.

The entire subject of fetal and neonatal death has been recently summarized by Potter and Adair.¹ Important developments in the field of asphyxia by Yant and associates,² Courville,³ Schreiber,⁴ and others have revealed many unfortunate results from asphyxia other than death. The knowledge of the fact that permanent damage to the central nervous system can be caused by anoxia is leading to a revision of our concepts concerning the seriousness of asphyxia neonatorum in those infants who survive. Schreiber's⁴ statistics show that 70 per cent of a group of 500 individuals with evidence of neurologic disease of obstetric origin had asphyxia at birth. DeLee⁵ has long stressed the importance of observing these individuals in later life.

With the improvement in medical records and statistics, we should be able eventually to observe the asphyxiated infant and its ultimate fate. From the few figures available, the incidence of asphyxia is usually from three to five times greater than that of neonatal death. This makes the group under consideration much larger than the neonatal death group alone and probably embraces between 15 and 25 per cent of all infants.

At the inception of this study, little could be found in the literature concerning statistical evaluation of the many etiologic factors of asphyxia neonatorum. Since then Cole, Kimball and Daniels⁶ have analyzed 5,000 consecutive deliveries on the basis of the etiologic factors of asphyxia. Prior to this report most of the literature was concerned with the evaluation of various analgesics and their merits as demonstrated by relationship to the incidence of asphyxia neonatorum. A tabulation of the literature concerning pain relief in labor listed over 400 such articles by 1930; hundreds more have appeared since then. Thus, a critical review of the literature is all but impossible, yet from these reports, the consensus is to date that no one has found a pain-relieving drug which does not reflect itself by increasing asphyxia neonatorum. History indicates that many drugs have been in favor for a short or longer period of time as ideal analgesics, only to fall into ill repute by the test of time. The case of "twilight sleep" is a notable one. In general, there has been too much emphasis placed on the type of drug used and too little knowledge employed in the correct use of any chosen one. The pivotal point has been aptly stated by Clifford and Irving⁷ who state that no method of obstetrical analgesia . . . "is without some unfavorable influence on the fetus . . . and the ultimate fate of the present methods of analgesia may hinge on the price the infant must pay for the mother's comfort."

and disadvantages were found with the use of completed records; difficulty was encountered occasionally when there was incomplete data. This was offset by the data being entirely impersonal and unbiased. Twenty cases were not used because of lack of data or because the pregnancy was of less than twenty-eight weeks' duration. There was some question as to the proper classification of stillbirths. Inasmuch as many stillbirths are due to asphyxia in labor, only infants dead at the onset of labor (absent fetal heart tones) were excluded. There were 24 of these, 18 of which were found to be macerated at birth.

RESULTS

On the basis of the previously mentioned classification, the following results were obtained from a study of 1,982 infants: No asphyxia, 85 per cent (1,684 cases); mild asphyxia, 6.8 per cent (134 cases); moderate asphyxia, 6.0 per cent (120 cases); severe asphyxia, 2.2 per cent (44 cases). Those classified as no asphyxia had normal respiratory function at birth. The "mild" group were those

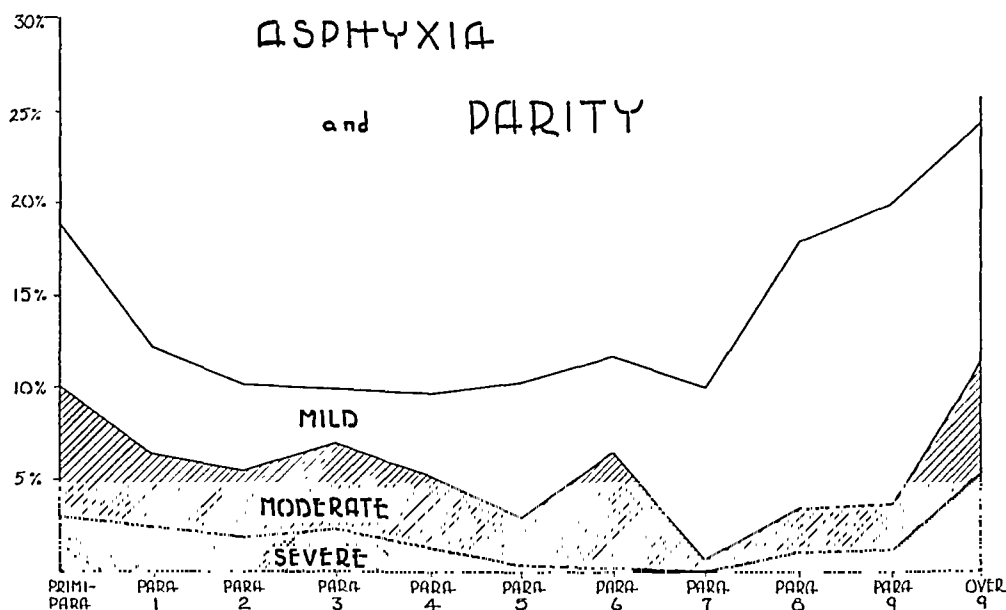


Fig. 1.—The incidence of mild, moderate, and severe asphyxia neonatorum in 890 primiparas and 1,092 multiparas.

apparently not seriously involved and would be considered by many observers as normal infants. To a certain extent the "moderate" group roughly corresponds to the old classification of asphyxia livida. The "severe" group contains those previously known as asphyxia pallida but may also contain those with asphyxia and cyanosis.

Parity.—As was expected, the primiparas have nearly twice the incidence of asphyxia that multiparas have, primiparas 18.9 per cent and multiparas 11.7 per cent. Unexpected were the results found in a comparison of the various degrees of parity. The optimum parity occurred with the fourth or fifth child, this was followed by an increase beginning with the eighth pregnancy (Fig. 1). This apparently coincides with the increase in age noted by Cole and others.⁶

Prenatal Complications.—This was one of the important factors noted in this series. An unusually high percentage of complicated obstetric cases are treated at this hospital. Out of 1,684 deliveries, 595, or 30 per cent, had some prenatal complications. The total percentage of asphyxia was over twice as great in these in-

The opinions, experience, and individual reactions of the obstetrician result in diverse conceptions, first as to what constitutes asphyxia neonatorum, and second, as to the need for resuscitative methods. The perfectly normal newborn infant takes its first breath as delivery is completed or immediately afterwards. This usually occurs within ten or twenty seconds after birth and certainly should occur within a minute. After this, the respiratory passages contain enough air to permit the characteristic loud, vigorous, and lusty cry. Any infant that fails to do this is not physiologically normal at birth, and therefore should be classified as asphyxiated. These infants with abnormal respiratory function manifest one or more of the readily observed signs in Table I.

This classification was the basis for the present study. Occasionally some difficulty was encountered in the classification of mild asphyxia due to incomplete data. This has led to the practice now employed at every delivery; namely, the accurate recording, in seconds, of the length of time from birth until the first breath and also until the characteristic vigorous lusty cry. Both of these are readily observed and constitute end points for judgment of the degree of asphyxia. The actual timing of the institution and duration of resuscitation is also important.

TABLE I. CLASSIFICATION OF ASPHYXIA NEONATORUM AS USED IN THIS STUDY

PHYSICAL SIGNS		NO ASPHYXIA	MILD ASPHYXIA	MODERATE ASPHYXIA	SEVERE* ASPHYXIA
Respiratory	Onset Respiration	Spontaneous Immediate	Spontaneous Oligopnea 1-5 min.	Delayed Apnea 5-15 min.	Delayed Apnea over 15 min.
	Resuscitation	None	None	Tracheal tube or mouth-to-mouth	Tracheal tube or mouth-to-mouth
Activity	Cry	Vigorous Lusty	Delayed Vigorous Lusty	Delayed Weak	Weak or absent
Cyanosis		None	Mild	Moderate	Severe or pallor
Muscular activity		Vigorous Active	Sluggish	Depressed	Flaccid and relaxed
Pallor and/or shock		None	None	None	Present

*All infants alive at onset of labor but who died during labor are included in this group.

In the following clinical-statistical study of over 2,000 consecutive deliveries, we shall attempt to tabulate and evaluate the frequency, severity, and combined effects of some of the etiologic factors that alter the normal respiratory function of the infant at birth. All of the patients were delivered on the obstetric floor of this hospital; they were both private and ward patients, but every case was under the direct supervision of attending staff or trained residents. This fact lends accuracy and uniformity to the data. The results were compiled by a careful study of the completed obstetric record, infant record, and anesthetic record, and then transferred to punch cards. From these cards practically unlimited statistical analyses were possible. Both advantages

logical method, being well aware of the inaccuracy of gestational age based on menstrual history alone. All infants born before the twenty-eighth week were excluded. Table II shows the incidence of asphyxia and neonatal death in relation to maturity.

Maturity as determined by gestational age has a profound effect on the incidence of asphyxia, and asphyxia in turn is followed by an increase of the neonatal death rate. For example, a 28-week-old infant born without asphyxia has a better chance of survival than a term infant born with severe asphyxia. Asphyxia is increased in the premature following the use of nonvolatile analgesics and is of great importance, as can be seen from Fig. 3. The question of analgesia will be further discussed subsequently.

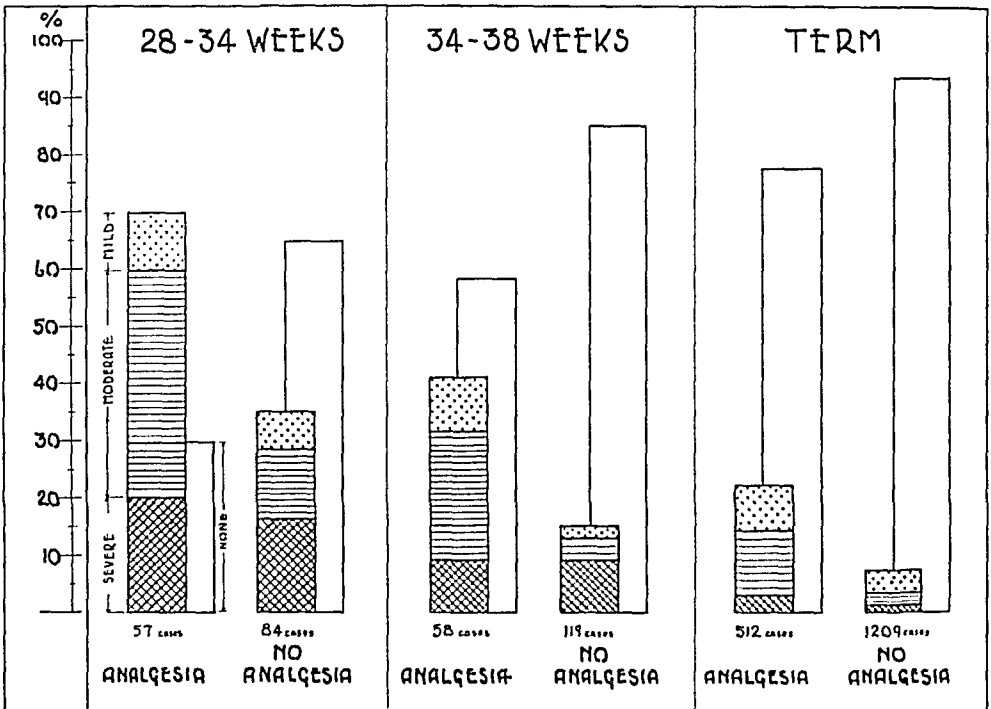


Fig. 3.—Shows the effect of all nonvolatile analgesics, mostly opiates, in relation to maturity. The combination of prematurity and analgesia result in an unusually high percentage of asphyxia neonatorum. The increase is most marked in the moderate and severe degrees.

Presentation and Position.—As would be expected breech presentations were associated with double the incidence of asphyxia found in cephalic presentations, the figures being 27 per cent and 14 per cent, respectively. There was also a relation to position as well. The two occipitoanterior positions, R.O.A. and L.O.A., were practically identical in incidence of asphyxia. All occipitotransverse and posterior

TABLE III. THE RELATION OF ASPHYXIA TO PRESENTATION AND POSITION

POSITION AND PRESENTATION	NO. OF INFANTS	NO ASPHYX-IA	MILD ASPHYX-IA	MODER-ATE ASPHYX-IA	SEVERE ASPHYX-IA
All occipitoanterior positions—L.O.A. and R.O.A.	1334	88.5	6.0	5.0	1.5
All occipitotransverse and posterior positions—L.O.T., L.O.P., R.O.T., R.O.P.	518	81.0	7.0	8.5	3.5
Breech	80	74.5	11.0	9.0	5.5

dividuals, being 26 per cent while the uncomplicated cases had only 11 per cent asphyxia. There is a wide variation in the frequency of asphyxia, depending on the type of complication present. In classifying individuals having more than one prenatal complication, the most significant one was chosen. For example, toxemia would receive preference over the common cold. These results are graphically recorded in Fig. 2.

Maturity.—Most reports considering maturity are usually based on the weight of the newborn infant as the criterion of maturity, or on a combination of weight and gestational age. Inasmuch as accurate determination of weight before birth is impossible and even the estimation of weight is subject to gross inaccuracies, we have classified maturity on the basis of gestational age alone. In a survey primarily intended to permit the evaluation of the unborn infant, this seems to be a

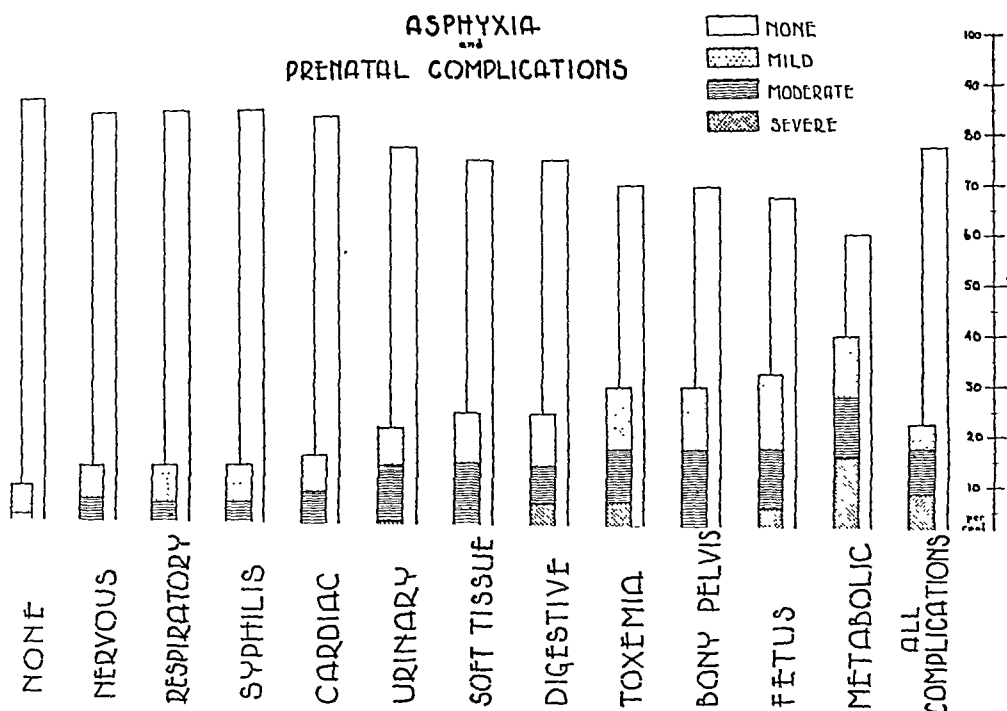


Fig. 2.—Shows the effect of prenatal complications on asphyxia neonatorum. Nervous system complications (35 cases) include paralysis, psychosis and others. Respiratory diseases (69 cases) are minor, such as common cold, and major, such as tuberculosis, bronchitis, and pleuritis. Syphilis 38 cases. Cardiac disease (63 cases) includes all types of heart disease in all stages of compensation. Urinary complications (47 cases) are primarily pyelitis. Soft tissue anomalies (39 cases) are those of the pelvis and include fibroids, cysts, prolapse and others. Digestive disturbances (28 cases) are colitis, appendicitis, cholecystitis, hepatitis, and others. Late toxemias 129 cases. Contracted pelvis 120 cases. Metabolic diseases (18 cases) were either diabetes mellitus or hyperthyroidism.

TABLE II. A COMPARISON OF THE FREQUENCY AND SEVERITY OF ASPHYXIA AND NEONATAL MORTALITY DURING VARIOUS GESTATIONAL AGES

GESTA- TIONAL AGE IN WEEKS	NO. OF IN- FANTS	NO ASPHYXIA		MILD ASPHYXIA		MODERATE ASPHYXIA		SEVERE ASPHYXIA	
		% NOT AS- PHYXI- ATED	% OF NEO- NATAL DEATHS	% OF AS- PHYXIA	% OF NEO- NATAL DEATHS	% OF AS- PHYXIA	% OF NEO- NATAL DEATHS	% OF AS- PHYXIA	% OF NEO- NATAL DEATHS
28	33	48.5	50.0	15	80	30.0	90	6.5	100
32	50	58.0	17.0	18	11	16.0	50	8.0	100
36	177	76.5	3.0	9	0	10.5	20	4.0	43
40	1,655	86.0	1.5	6	0	5.0	10	1.75	66
40+	67	85.5	0.0	8	0	5.0	30	1.5	100

Type of Delivery.—Operative delivery increased asphyxia. Out of 636 operative deliveries 159, or 25 per cent, of the infants had asphyxia, while only 134, or 10 per cent, of those from 1,346 spontaneous deliveries were similarly affected. We recognize that operative delivery is frequently indicated, regardless of the danger of asphyxia, and at times it may actually decrease the incidence of asphyxia when there is a failing fetal heart rate which fails to respond to maternal oxygen therapy,¹⁷ or where there is premature separation of the placenta, prolapse of the cord, or similar disturbances. Table IV shows that operative deliveries per se cause increase in asphyxia neonatorum; for example, the rate of asphyxia in spontaneous deliveries where no nonvolatile analgesics have been given is 8.5 per cent, while following low forceps deliveries under similar circumstances, the rate is 11 per cent. Yet the combination of operative delivery and analgesics greatly increase the incidence and severity of asphyxia.

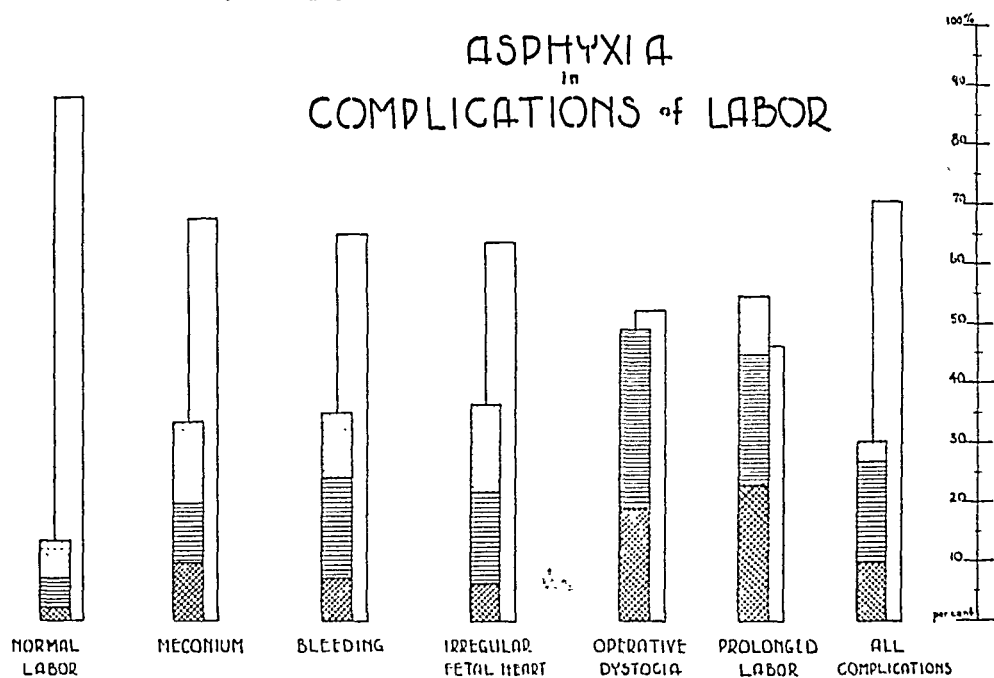


Fig. 5.—Shows some of the dangerous complications of labor in regard to asphyxia neonatorum. Meconium was observed in 37 cases exclusive of breech presentation. Bleeding was noted in 47 cases of placenta previa and premature separation of the placenta. Marked irregularity and slowing of the fetal heart was found in 62 cases. Prolonged labor meant a labor of over thirty-six hours, this present in 26 cases. Operative dystocia was present in 25 cases.

Complications of Labor.—In addition to prenatal complications, we have another group of complications active during labor and more or less intimately associated with it. There were 292 of these cases; however, only 238, or 12 per cent, were of possible effect on the fetus. Those excluded were such factors as post-partum hemorrhage before delivery of the placenta, manual removal of the placenta, and others. Complications of labor include the often mentioned factors of cord prolapse, knots in the cord, and tetanic uterus. These are usually mentioned in textbooks as frequently occurring factors, and one is led to believe that they are responsible for much fetal asphyxia. Actually they occurred in only 5.5 per cent of the 238 complicated labors, or 0.65 per cent of our entire series. When they were present, the incidence of asphyxia was 46 per cent (occult prolapse of cord not included). As will be seen in Fig. 5, there are other complications occurring in greater frequency which are followed by as severe or even more severe asphyxia.

Analgesics.—Unless specifically otherwise stated, the term analgesics is used in this paper to signify drugs other than inhalation analgesics given during labor. The

positions were also similar but in these the incidence of asphyxia was increased 33 per cent and the severe type of asphyxia doubled. The results are summarized in Table III. The results are not surprising when one considers that in this series occipitoposterior positions were accompanied by a threefold increase in incidence of operative delivery, a twofold increase in the administration of nonvolatile analgesics and a 20 per cent and 30 per cent increase in the duration of the first and second stages of labor, respectively. Regardless of the factors that cause the increase in asphyxia, the fact remains that the prognosis for the infant is definitely worse in the case of occipitoposterior and breech presentations.

Duration of Labor.—This is divided into first and second stages as follows: *First stage:* With the exception of precipitate labors and prolonged labors the results are not striking. Because of the marked variation in length of labor in primiparas and multiparas, they are considered separately, yet the results are not significantly different. As can be readily seen from Fig. 4 asphyxia is greatest in labors of less than three to four hours and in those of over thirty hours. The optimum duration of the first stage as regards asphyxia is one of about five to seven

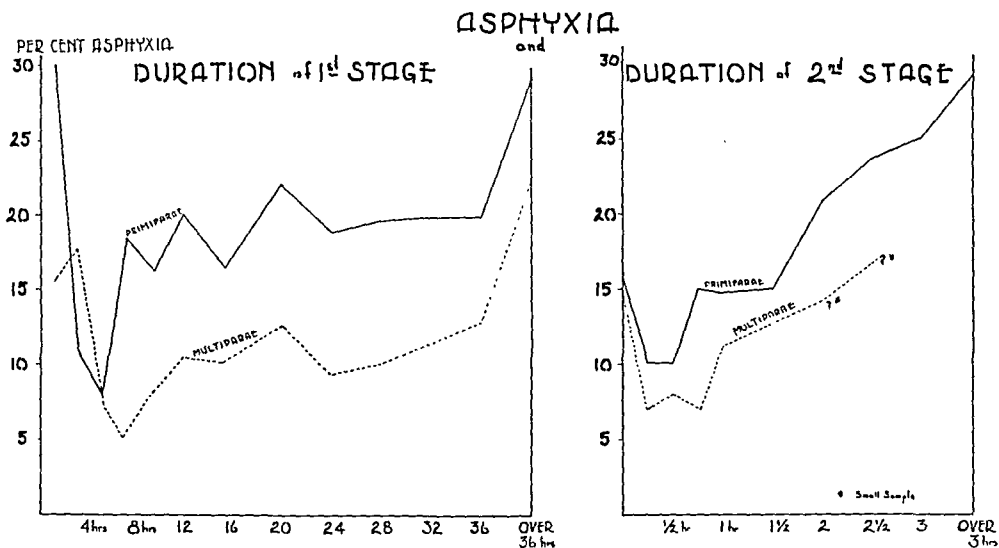


Fig. 4.—Unusually short or prolonged first and second stages result in increased asphyxia neonatorum. The general trend is the same in both primiparas and multiparas. A first stage of over thirty-six hours or a second stage of over one and one-half hours is accompanied by a rapid increase in asphyxia.

hours for both primiparas and multiparas; yet the average duration of the first stage in primiparas was thirteen hours and thirty-six minutes, and 41 per cent of the labors occurred in the nine- to fifteen-hour period. The multiparas had an average duration of the first stage of seven hours and thirty minutes and 42 per cent of the labors took place during the five- to seven-hour period. Thus, multiparas tend to have a first stage of more nearly the optimum duration. Prolonged labor carries a high degree of asphyxia as will be seen under the consideration of complications of labor. *Second stage:* The same general results are observed here. The precipitate deliveries are followed by a mild increase in asphyxia neonatorum but the greater danger follows the long second stage. Comparing the primiparas and the multiparas as before, we find that the primiparas have an average duration of second stage of one hour and seventeen minutes with 46.5 per cent deliveries occurring in the one- and one-and-one-half-hour groups. The average duration in the multiparas was forty minutes, with 69 per cent of the deliveries in the fifteen to forty-five-minute periods. Only 26.5 per cent of the primiparas delivered at the optimum period. Note the relatively rapid increase in the rate of asphyxia after the second stage has exceeded one and one-half hours in length (Fig. 4).

"others" are those who received small doses of barbiturates, codeine, etc., a small heterogeneous group of little significance.

From these figures, it would seem that morphine produces greater asphyxia neonatorum than heroin. A repeat dose of heroin produces about the same asphyxia as does morphine. The increase in asphyxia following heroin occurs in the moderate group; for the remainder, it occurs in the severe groups.

In order to exclude and to evaluate the factor of trauma, we have analyzed the various drugs in relation to spontaneous, low forceps deliveries, and then all operative deliveries in relation to total asphyxia. From Table VI we see that in the case of spontaneous delivery heroin has a definite advantage over morphine, but in the operative deliveries this advantage is lost. Furthermore, there is a definite danger in repeating any opiate, even heroin, though it is known to be one of the most rapidly acting ones.⁶ In the same table we have combined the results of various analgesics in the premature infants.

TABLE VI. THE INCIDENCE OF ASPHYXIA IN RELATION TO TYPE OF DELIVERY, MATURITY, AND TYPE OF ANALGESIC

TYPE OF ANALGESICS	NO. OF CASES	PER CENT IN SPONT.	PER CENT IN LOW FORCEPS	PER CENT IN ALL OPERATIVE	PER CENT IN TERM INFANTS	PER CENT IN ALL PREMATURES
None	1,384	8.5	11.0	15	8	22
Heroin	344	16.0	28.5	29	18	40
Heroin repeated	47	22.0	30.5	39	21	64
Morphine alone or with scopolamine	72	31.5	29.5	28	26	50
Scopolamine	95	0	0	40	34	69
Others	40	22.0	10.0	20	6	40

In the relation to maturity, there is apparently no specificity as far as the drugs used were concerned. Asphyxia increased markedly in prematures following all types of analgesics. Space does not permit a complete analysis of maturity and types of asphyxia but the increase occurs in the "moderate" group in the prematures.

One cannot avoid the old question of the interrelationship of asphyxia, length of labor and analgesic drugs, Are they independent, related, or synergistic? We have previously stated that asphyxia increased after rapid labors. However, when these figures are analyzed on a basis of analgesia, we find that only the patients having had analgesics show this effect, while those with no analgesia had no increase in asphyxia following a short first stage (Fig. 6). The asphyxia is due to an error in judgment in administering opiates to patients that deliver within five hours after the onset of labor. Prolonged labor apparently causes increased asphyxia whether analgesics are given or not, but the total figures are too small for accurate interpretation. The situation during the second stage of labor is similar as regards the cases delivering within fifteen minutes, asphyxia being apparently due to analgesia and not to the rapid labor. However, a reversal is noted in relation to prolongation of the second stage. Here asphyxia neonatorum was greater when the mothers were given analgesics. The optimum length of the second stage of labor is about thirty minutes, and at this particular time, there is little difference between those receiving analgesia and those without it.

Induction of Labor.—Medical induction of labor, using enemas and quinine, 15 to 30 gr., and posterior pituitary, had apparently little effect on the incidence of asphyxia. Sadler and others¹⁹ described deleterious effects on the infant from quinine given for medical induction. The total asphyxia in our 1,656 noninduced cases was 13.6 per cent and in the 311 medically induced cases was 15 per cent.

Anesthesia and Analgesia.—Of the 1,982 cases 1,806 had some form of inhalation analgesia or anesthesia; 1,504 patients had nitrous oxide-oxygen intermittent analgesia with pains; 142 had no inhalation analgesia or anesthesia; 350 had an-

TABLE IV. A COMPARISON BETWEEN THE TYPE OF DELIVERY, THE USE OF ANALGESICS,* AND THE INCIDENCE AND SEVERITY OF ASPHYXIA

TYPE OF DELIVERY	NO. OF CASES	NO ASPHYXIA %		MILD ASPHYXIA %		MOD. ASPHYXIA %		SEVERE ASPHYXIA %	
		NO ANALG.	WITH ANALG.	NO ANALG.	WITH ANALG.	NO ANALG.	WITH† ANALG.	NO ANALG.	WITH ANALG.
Spontaneous	1,329	91.5	82.5	5.5	6.0	2.0	10.0	0.7	1.0
Low forceps	349	89.0	73.0	5.0	10.5	4.0	13.5	2.3	2.5
Mid-forceps	36	85.5	67.0	0.0	0.0	9.5	33.0	4.5	5.5
Cesarean section	159	78.0	60.0	13.5	11.0	4.0	21.5	4.0	6.5
Breech	80	77.5	68.5	7.5	12.5	7.5	12.5	7.5	8.0
Version	24	44.0	67.0	25.0	0.0	25.0	0.0	6.0	33.0

*Types of analgesics are discussed later.

†Greatest increase in this group.

relationship between analgesics and asphyxia neonatorum has been the subject of much controversial literature for years. It is not the purpose of this paper to discuss the advantages or disadvantages of any of these analgesics as they effect maternal amnesia and pain relief. The relationship of certain of these agents to asphyxia neonatorum will be shown. Recent studies of morphine by Shute and Davis,¹⁰ of barbiturates by Clifford and Irving,⁷ and by Lewis,¹¹ of scopolamine by Cole and associates⁶ have summarized the effects of these drugs on asphyxia neonatorum. Our figures tend to confirm some of these observations and in addition present results following the use of heroin. We have deliberately avoided a consideration of the time factor which exists between the time of drug administration and delivery for two reasons: In the first place, it is now well known that the time element is of marked importance in the administration of morphine and closely allied drugs¹⁰ and is of considerable less significance in the case of barbiturates.⁷ Second, we always attempt to estimate this time and govern our administration of opiates so that they antecede delivery by at least four hours. In the majority of cases, this is possible. When failures due to inaccurate timing occur, they can be charged to the opiates, because the time factor then becomes a quality of the drug, assuming of course that reasonable obstetric judgment is used in administration. Usually $\frac{1}{12}$ gr. of heroin was the average dose. The morphine dosage varied from $\frac{1}{8}$ to $\frac{1}{4}$ gr. Scopolamine was from $\frac{1}{150}$ to $\frac{1}{200}$ gr., was not repeated, and was used alone only as a premedication for cesarean section. Analgesics administered twelve hours or longer before delivery were excluded. In Table V we find the general results for each of the above-mentioned drugs, included under the title

TABLE V. THE TYPES OF PAIN-RELIEVING DRUGS USED AND THE FREQUENCY AND SEVERITY OF ASPHYXIA NEONATORUM FOLLOWING THEIR USE

TYPE OF DRUG	NO. OF CASES	NO ASPHYXIA %	MILD ASPHYXIA %	MODERATE ASPHYXIA %	SEVERE ASPHYXIA %
None	1,384	89	6.0	3	2.0
Heroin	344	80	7.0	11	2.0
Heroin repeated	47	68	8.5	17	6.5
Morphine alone or with scopolamine	72	70	12.0	12	6.0
Scopolamine*	95	60	13.0	21	6.0
Others	40	87	3.0	5	5.0

*Premedication for cesarean section.

Infant Complications.—Exclusive of congenital malformations, 41.5 per cent of the asphyxiated infants had some type of postnatal complication, while only 17 per cent of the nonasphyxiated babies had complications. These were all inclusive in their nature, such as trauma, both major and minor; all types of respiratory infections, atelectasis, cough, mucus, etc.; excessive regurgitation; unusual irritability or lethargy, etc. We were able to follow over half the infants for one year or longer, and in this group, there were 10 with permanent central nervous defects, of which 4 had severe asphyxia at birth and one had moderate asphyxia. One striking case can be mentioned: An elective cesarean section was done at term before onset of labor in a patient with contracted pelvis but otherwise normal. Technical difficulties encountered during anesthesia were responsible for severe anoxia of the mother and fetus; the infant was deeply asphyxiated at delivery and had a stormy postnatal course. Later encephalograms revealed a generalized cortical atrophy, and because of mental deficiency, the infant was institutionalized.

DISCUSSION

For many years it has been customary to classify surgical patients as to their surgical risk; and on this basis, the choice of surgical procedure, the method of anesthesia, and type of premedication are made. This classification has not been in general use in obstetrics where the complexities of the problem are multiplied by the necessity of evaluating two patients, mother and baby. In the past, the mother has usually received the major portion of the attention, frequently at the unnecessary expense of the fetus. There is an unfortunate tendency to generalize in the treatment of obstetric patients. Such statements as "I give all my primiparas morphine, $\frac{1}{4}$ gr.," "all multiparas receive 6 gr. of nembutal" or "all primiparas are delivered by forceps with ether anesthesia" are frequently made. Complete individualization should be the rule, not only for the mother but also for the fetus. Only by combining our knowledge of these two factors in their proper relation can we arrive at a rational course of therapy. The proper proportions between factors that favor the safety and comfort of the mother but endanger the fetus can be determined only by obstetric judgment.

Just as the mother is evaluated as an obstetric risk, so should the fetus be considered from the standpoint of *asphyxial risk*. There are many factors that increase the incidence of asphyxia neonatorum. On the basis of frequency and severity, we have found them to be prematurity, especially when combined with nonvolatile analgesics; prenatal complications, particularly toxemias, hyperthyroidism, diabetes, contracted pelvis, multiple pregnancy, hydramnios, pyelitis, and pelvic soft tissue abnormalities. The most dangerous complications of labor are prolonged labor, operative dystocia, placenta previa, and premature separation of the placenta, irregularities of the fetal heart rate. Operative delivery causes some increase in asphyxia, but when combined with opiates greatly increased the asphyxia. From the nature of these etiologic factors, it is obvious that good prenatal care is a potent factor in limiting asphyxia neonatorum. Prematurity and various prenatal complications need to be promptly recognized and treated. The remainder of the problem can be improved by individualizing the conduct of labor both as it affects the mother and the infant in utero. The diagnosis of fetal anoxia in utero by fetal heart arrhythmia and treatment by maternal oxygen administration should be kept in mind.¹⁷

esthesia without analgesia; and 477 of the 1,504 patients having analgesia had subsequent anesthesia with delivery. A complete study of gas analgesia and anesthesia in relation to asphyxia has been made and will appear in a subsequent publication. In general, the results show that intermittent nitrous oxide-oxygen analgesia properly used is associated with a low incidence of asphyxia neonatorum. General anesthesia as given for operative delivery may be associated with increased asphyxia, that this was not due to trauma alone was demonstrated in the cases of cesarean section where the rate was equally as high.

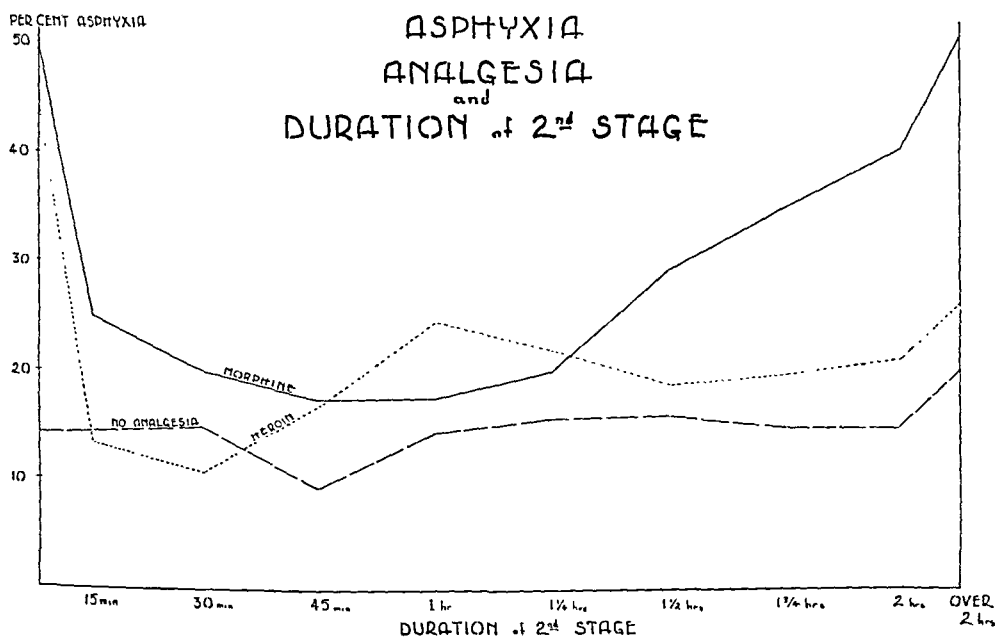
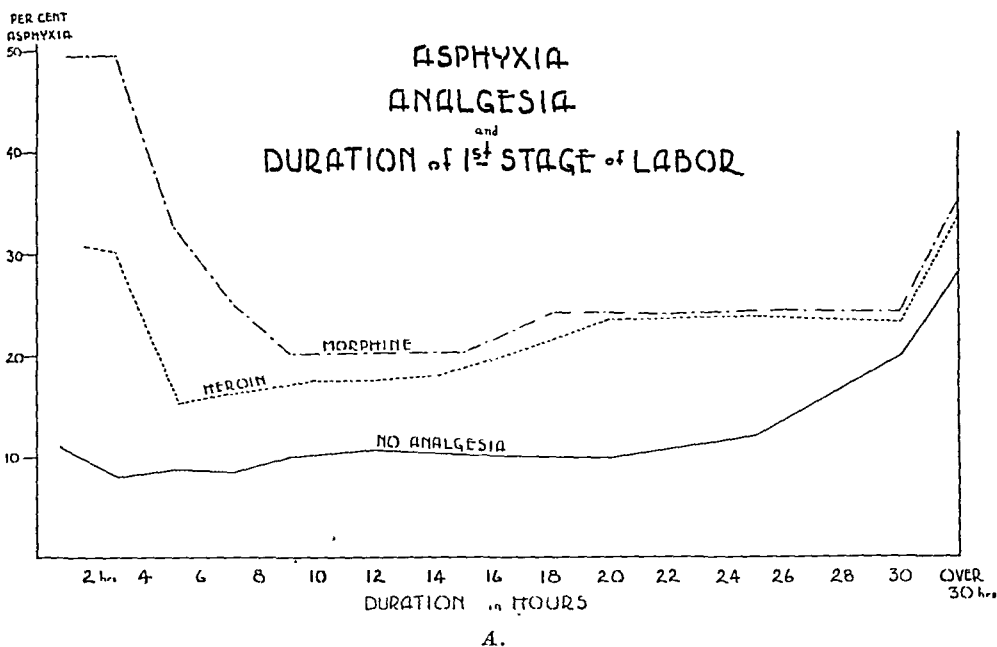


Fig. 6.—Prolonged labor, both first (A) and second stage (B), is accompanied by increased asphyxia neonatorum. Rapid labors are not followed by increased asphyxia neonatorum except when heroin or morphine is given for analgesia, in which case delivery occurs before the depressant effects of the drug are lost.

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THE VALUE OF CALCIUM IN LABOR AND IN UTERINE INERTIA*

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INVESTIGATION of the effects of the intravenous administration of calcium salts in labor was undertaken for two reasons: First, we questioned whether calcium might relieve the pain of uterine contractions; and, second, we wished to determine the effect of calcium on the contractibility of the human uterus during labor.

The basis for the speculation that calcium might relieve the pains of labor was the relief of pain that had been obtained by means of this treatment in lead colic,⁴ gallstone colic,²² acute epididymitis,^{23, 35} acute salpingitis,³⁰ and certain malignant conditions.⁵ Muscle cramps which occur during pregnancy commonly yield readily to calcium administered orally.^{17, 18, 26, 32} Hence, it seemed reasonable to suppose that calcium might relieve the spasmodic uterine pain of labor, thus permitting the uterus to contract painlessly, as do other muscles of the body. The mechanism of the action of calcium on the body tissues may be explained by the statement that it decreases the permeability^{11, 13} of cells and thus lessens the excitability of striated and smooth muscles and also somatic and autonomic nerves. Since it is known that section of the presacral (sympathetic) nerve plexus will relieve pain caused by the contracting uterus during labor,¹⁶ it was hoped that calcium, by reducing the excitability of the sympathetic nerves, might have a similar effect. Empirically, calcium has been used as one of the agents for the relief of dysmenorrhea. Kraus and Zondek, on the other hand, have reported that an excess of calcium in the body will produce certain effects similar to those produced by stimulation of the sympathetic nerves. If this is true, calcium would not relieve the pains of labor. Hartley^{17, 18} wrote that the oral administration of calcium to a woman during pregnancy would definitely shorten the period of labor. Richardson^{32, 33} showed that viosterol administered during pregnancy would increase the value for calcium in the blood and that such a procedure would subsequently result in a shortening of the average

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SUMMARY AND CONCLUSIONS

The rational approach to the problem of asphyxia neonatorum is by prophylaxis, notwithstanding the voluminous literature concerned with therapeutic methods. Analysis of the etiologic factors of asphyxia as seen in 2,006 consecutively born infants reveal the following:

1. *Parity*: Primiparas had 18.9 per cent asphyxiated babies while the multiparas had 11 per cent, but after the eighth child asphyxia increased with parity.

2. *Prenatal Complications*: Their presence increased asphyxia from 11 per cent in the uncomplicated to 26 per cent in the complicated cases. Metabolic diseases, soft and bony pelvic abnormalities, toxemias, multiple pregnancy, and diseases of the gastrointestinal and urinary tracts were followed by the greatest incidence of asphyxia.

3. *Prematurity*: The greatest single factor in our series, most dangerous when combined with analgesic drugs where as high as 70 per cent asphyxia was found.

4. *Presentation and Position*: Breech presentation was followed by 27 per cent asphyxia, occiput posteriors by 18.2 per cent, and occiput anteriors by 12.2 per cent asphyxia.

5. *Duration of Labor*: Only when the first stage was over thirty hours was there a marked increase in asphyxia. A second stage of over one and one-half hours was followed by a progressive increase in asphyxia.

6. *Type of Delivery and Trauma*: Spontaneous deliveries showed a rate of 10 per cent asphyxia while operative deliveries were followed by 25 per cent asphyxia. Use of nonvolatile analgesics before operative delivery greatly increased asphyxia.

7. *Complications of Labor*: Variations in rate and rhythm of the fetal heart, maternal bleeding, cord prolapse, operative dystocia, and prolonged labor were accompanied by asphyxia neonatorum varying from 35 to 55 per cent. Uncomplicated labor resulted in 12 per cent asphyxiated infants.

8. *Analgesics*: Analgesics studied were primarily heroin and morphine with or without scopolamine. In spontaneous deliveries heroin stood midway between the group receiving no sedation and those receiving morphine. This advantage was lost following operative deliveries. Repeated administration of heroin was followed by increased asphyxia in spite of its rapid action.

9. *Medical Induction of Labor*: This had little effect on asphyxia.

10. *Infant Complications*: They increased from 17 per cent to 45 per cent when the infant was asphyxiated at birth. Ten cases of permanent central nervous system damage were found; five of these infants had asphyxia at birth.

The individual evaluation of every obstetric case on the basis of fetal asphyxial risk, as well as a general obstetric risk, is advised. Prenatal care and conduct of labor on this basis should result in a substantial reduction of the incidence of asphyxia neonatorum.

Fig. 2. After completing this work, we learned of the Lorand tocograph and of the excellent tracings of uterine contractions which Murphy obtained with this device. Before calcium was administered, a final check was made of dilatation of the cervix (by rectal examination), blood pressure, pulse, and respiration (Table I). A sample of blood was then drawn from the median basilic vein for determination of calcium. With the needle still in place, the syringe containing a 10 per cent, or sometimes, a 20 per cent, solution of calcium gluconate was attached, and slow administration of the solution was begun. Four cubic centimeters per minute was considered to be the maximal rate at which the solution could be administered with avoidance of un-

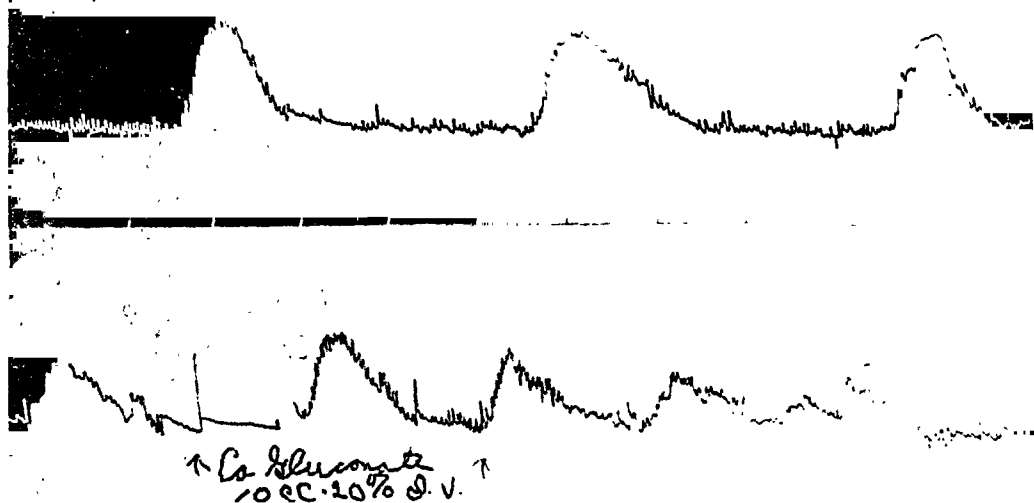


Fig. 1.—Reproduction of a kymographic tracing of the uterine contractions of Patient 14 (Table II) before and after the administration of 10 c.c. of a 20 per cent solution of calcium gluconate. The two lower lines are immediate continuations of the two upper lines. Large curves represent uterine contractions; frequent, small excursions represent abdominal respiratory movements. The decreased interval occurring between uterine contractions after administration of calcium gluconate is clearly shown.

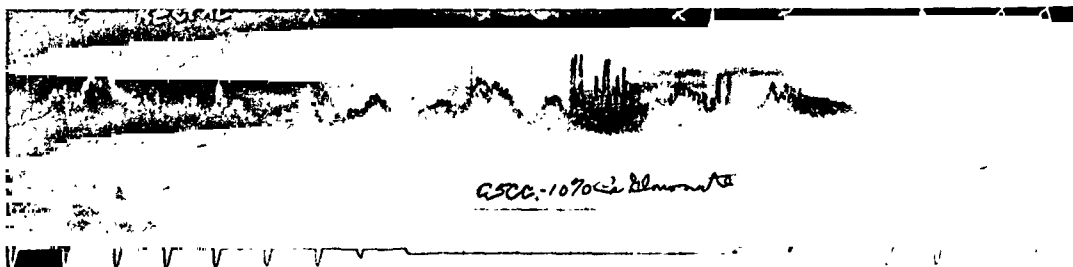


Fig. 2.—Reproduction of a kymographic tracing of the uterine contractions and occurrence of labor pains of Patient 19 (Table II) before and after the administration of 25 c.c. of a 10 per cent solution of calcium gluconate. Large curves represent uterine contractions and each \times at the upper margin of the tracing indicates occurrence of a subjective labor pain. Immediate increase in the frequency of uterine contractions after the administration of calcium gluconate is evident.

pleasant side reactions. The dose to be administered was problematic. Certainly, the investigator would hesitate to use the dose that has been used in experiments with animals: 10 to 30 mg. of calcium ion per kilogram of body weight. The lethal dose of calcium, injected intravenously in the form of an 8.4 per cent solution of calcium gluconate, at the rate of 4 c.c. per minute, is 185 ± 57 mg. of calcium ion per kilogram of weight of the animal.²⁵ Actually, from 1.24 to 5.08 mg. of calcium ion per kilogram of body weight was used in the present study (Table II). Transposed into terms of calcium gluconate, these values would vary from 10 c.c.

labor of primiparas of from nineteen hours to six hours. Baq and his associate, in studies on cats, demonstrated that the administration of calcium would cause contraction of the denervated, nonpregnant uterus, but that such contraction would occur only when the adrenal vessels were ligated. After the injection of ergotamine had depressed intestinal muscles so that contractions no longer occurred, the administration of calcium permitted subsequent doses of ergotamine to stimulate the intestine again, according to Salant and Parkins. Rozen and Perussé observed effects similar to those experienced with ergotamine and calcium by administering magnesium chloride and calcium lactate orally. Calcium chloride administered intravenously, however, caused loss of intestinal tonus and vomiting. They thought these actions to be central effects, because contraction of strips of gastric muscle has been shown to be enhanced when such strips are immersed in a solution of calcium. Berg and associates said Billinghamer noted that the administration of epinephrine (which slows or stops uterine contractions⁹) would decrease the value for calcium in the blood. This action could be interpreted to mean that an increase in the content of calcium in the blood might increase uterine contractions. Fitzhugh and associates, searching for the pain-relieving mechanism of calcium in spasm of smooth muscle, found that calcium lessens intestinal motility, but does not stop it. Johnson injected calcium gluconate, both intravenously and intramuscularly, into nonpregnant, ovariectomized rabbits that had received daily doses of a preparation which contained estrogenic hormone. The intensity and frequency of the uterine contractions were increased. Danforth and Ivy, in studies on dogs and rabbits after they had given birth to young, determined that calcium not only stimulates the uterus, but that its presence is necessary for the stimulating effect of the oxytocic principle of the posterior lobe of the hypophysis (pitocin), ergonovine, and histamine. Wiessmann and Klippel said that Pieri administered calcium gluconate to a woman in labor and noted that labor terminated more rapidly than in other patients in whom calcium gluconate had not been employed. This is the only record we can find of the administration of calcium to a woman in labor, with the exception of the work of Bardenheuer, who did employ calcium but did not mention the effect of it on uterine contractions. Winkler and Vetter used a mixture of calcium and quinine in an attempt to induce labor.

MATERIAL

The 26 pregnant women who were observed in this study were on a private and semiprivate obstetric service. They were at or near term and were either in labor or were undergoing attempted induction of labor. These conditions made it impossible to complete observations concerning every patient. Calcium gluconate* was used exclusively in this work, because it is less irritating locally than other calcium salts.

METHOD

At first, calcium gluconate was administered when the patient complained of severe uterine pain. Later in the study the drug was administered when it appeared that the uterine contractions were ineffectual, infrequent, short, or weak. In 11 of the 26 cases, a graphic tracing was obtained of the uterine contractions, both before and after the administration of calcium. The tracing was made on a smoked-drum kymograph by a stylus activated by a tambour. Rubber tubing connected the tambour to an air-filled balloon placed on the patient's abdomen over the region of the uterine prominence. A snug abdominal binder provided counterpressure to the balloon. It was necessary for the patient to remain on her back so that a good tracing might be obtained. The kymograph was run for several minutes to make certain that uterine contractions were not affected by the binder. A tracing of the uterine contractions of Patient 14 (Tables I, II, and III) is shown in Fig. 1, and a similar tracing concerning Patient 19 (Tables I, II, and III) is shown in

*Supplied through the courtesy of Abbott Laboratories and of the Sandoz Chemical Works, Inc.

began to occur every minute. They lasted for sixty seconds, with increased intensity. Five minutes later cervical dilatation was complete. Spontaneous delivery of the infant occurred fifteen minutes after the administration of calcium.

CASE 4.—The patient (No. 24 in Table III) was 36 years old. She had had one child. She had been in labor eleven and one-half hours, and was experiencing weak, irregular contractions lasting sixty to 120 seconds, and occurring at intervals of five to nine minutes, when treatment was initiated. The infant's head was in the left occipital transverse position and the patient's cervix was dilated to 3 cm. Immediately after the administration of 20 c.c. of a 20 per cent solution of calcium gluconate, the contractions became strong, occurred every minute, and each contraction lasted sixty to seventy-five seconds. Spontaneous delivery of the child occurred two hours after calcium had been administered.

DISCUSSION

Twenty-three of the 26 patients experienced definite stimulation of the uterus, in the form of an increase in either frequency or intensity of contractions, or both, following the administration of calcium gluconate. One of the 26 patients (No. 5 in Table III), experienced no increase in stimulation of the uterus over that degree of stimulation which, commonly, would have occurred had she not received calcium gluconate. There was no change in uterine contractions after the administration of calcium, and the content of calcium in the blood did not increase twenty-six minutes after such administration. However, the intensity of uterine contractions increased markedly forty-five minutes after the injection of calcium and delivery of the child occurred spontaneously five hours later. The increase in uterine contractions was so transitory in two cases that it could not be considered a true stimulation. One patient (No. 15 in Table III) was not in labor; Braxton Hicks' contractions increased after injection of calcium, but she experienced no true labor pains. Another patient (No. 25 in Table III) also was not in labor. The medical induction of uterine contractions by means of castor oil and ten injections of the oxytocic principle of the posterior lobe of the hypophysis (pitocin), 2 minims at each injection at thirty-minute intervals, had been completed four hours previously, and she was experiencing mild pains every five minutes at the time we began treatment. After she had received calcium, the pains increased in frequency so that they occurred every three minutes, but they ceased after fifteen minutes. The value for calcium in the blood was low and did not increase much (Table II).

Of the 23 patients in whom treatment was successful, the increase in contractions was short lived in three. For the first patient (No. 6 in Table III) the increased contractions became irregular after the administration of $1\frac{1}{2}$ gr. (0.1 Gm.) of pentobarbital sodium. In the second patient (No. 8 in Table III), after the cervix had been dilated to a diameter of 6.5 cm., the increased contractions ceased for a period of eleven hours, after the administration of 3 gr. (0.2 Gm.) of pentobarbital sodium. The third patient (No. 16 in Table III) was not in labor. Uterine contractions increased for one and one-half hours, then decreased again and finally stopped.

In four additional cases of the 23 patients in whom treatment was successful, no progress toward the desired objective was noted, despite

of the 10 per cent solution, to 20 c.c. of the 20 per cent solution. Five minutes after the solution had been administered, the blood pressure and the pulse and respiratory rates were again checked, because the maximal changes in these factors are reputed to occur at this time (Table I). With a fresh, sterile needle and syringe a second sample of blood was taken for purposes of determination of calcium five to thirty minutes after the calcium had been injected. From one to eight hours later (usually four hours), a third specimen of blood was obtained for determination of calcium. Making of the tracing was continued for about one hour after the injection of calcium. The content of calcium in the blood was determined by means of the Clark-Collip modification of the Kramer-Tisdall method. Duplicate tests were performed on each specimen of blood.

RESULTS

Effect of Calcium Gluconate on Labor Pains and Uterine Contractions.—No relief of labor pains resulted from the injection of calcium. In fact, in many instances the intensity of the pain was increased.

The effect on uterine contractions was one of stimulation. Twenty-four of the 26 patients experienced an increase in the frequency of contractions. Fifteen of the 26 patients experienced an increase in the intensity of the contractions, and this number includes one patient for whom the contractions did not increase in frequency. The duration of each contraction was not changed much from what it is in the average labor. In no case did tetanic spasm of the uterus occur, such as frequently results from the administration of injudicious doses of the oxytocic principle of the posterior lobe of the hypophysis.

Four cases will be reported herein to depict the decided effect which may be obtained by the administration of calcium.

REPORT OF CASES

CASE 1.—The patient (No. 1 in Table III) was 45 years old. She had had four children. When the patient's cervix was dilated to 9 cm. and the infant's head was 2 cm. above the ischial spines in the left occipital transverse position, uterine contractions became weak. Each contraction lasted forty seconds, and the interval between contractions was five minutes. The patient was prepared for delivery and administration of a 20 per cent solution of calcium gluconate was begun; but, after only 4 c.c. had been given, the uterus contracted strongly for sixty seconds. After an interval of one minute another strong contraction occurred. These two contractions were sufficient to bring the infant down to and over the perineum in the left occipital anterior position.

CASE 2.—The patient (No. 18 in Table III) was 29 years old. She had had one child. She was experiencing pains that occurred every three to four minutes and lasted thirty to eighty seconds at the time that treatment was begun. The cervix was dilated to 3 cm. at the time 15 c.c. of a 20 per cent solution of calcium gluconate was administered. The contractions immediately began to increase in frequency, so that one occurred every one to one and one-half minutes. Each contraction lasted thirty to sixty seconds. Five minutes after the administration of calcium, the patient's cervix was dilated to a diameter of 8 cm. Spontaneous delivery of the child occurred one hour after calcium had been administered.

CASE 3.—The patient (No. 20 in Table III) was 25 years old. She had had one child. She was experiencing adequate uterine contractions every two minutes, and the duration of each contraction was thirty-five seconds. The cervix was dilated to 3 cm. Since this patient was encountered early in the series, at a time when the stimulating effect of calcium was not so well appreciated as it was later, she received 25 c.c. of a 10 per cent solution of calcium gluconate. Contractions immediately

(Table I), but even these patients experienced little nausea. Regurgitation was not considered to be an indication for discontinuance of injection of calcium.

The regurgitation which 5 of the 26 patients experienced (Table I) was accompanied by audible peristaltic sounds. This effect passed off rapidly. In no case did it persist after the needle had been withdrawn from the vein. Fitzhugh and associates noted that administration of calcium did not relax induced intestinal spasm in dogs, but that it did modify the peak of the spasmodic contractions. In its effect on the 5 patients who experienced regurgitation, calcium probably stimulated the intestinal muscle somewhat in the same manner that it does the uterine musculature.

Effect of Calcium Gluconate on Blood Pressure, Pulse, and Respiration.—In general, systolic and diastolic blood pressures and pulse pressure tended to show an increase when readings were made five minutes after injection of calcium (Table I). The rate of respiration did not change more than six per minute for any patient, and the increase and decrease was distributed approximately equally. Variation in the blood pressure and pulse after the injection of calcium was as inconclusive as that published by other investigators.^{4, 24, 30} Among those of our 26 patients concerning whom complete readings of blood pressure and pulse and respiratory rates were obtained (Table I), the change in systolic blood pressure varied from -14 to +27, and the average was +6.7, expressed in millimeters of mercury. Similarly, the change in diastolic blood pressure varied from -12 to +22, and the average was +4.4, expressed in millimeters of mercury. The change in pulse pressure varied from -14 to +24, and the average was +3.3. The change in the pulse rate varied between -20 and +12, and the average was -5.2, expressed in beats per minute. It is likely that labor pains modified these readings somewhat, although we attempted to take the readings in the intervals between pains. Another factor was the dosage employed. Lieberman, who administered 35 to 40 mg. of calcium ion per kilogram of body weight to dogs, wrote that there resulted a decrease of 20 to 40 beats per minute in pulse rate, and an increase of 20 mm. of mercury in systolic blood pressure. Our readings, however, concerned human beings who received from 2.18 to 5.08 mg. of calcium ion per kilogram of body weight.

A vasomotor wave, characterized by the subjective feeling of warmth in the patient's skin, could be induced at will by rapid injection of solution of calcium gluconate. This symptom was not a cause for complaint if the rate of injection was 4 c.c. per minute, or less, of the 10 per cent solution.

Effect of Calcium Gluconate on Blood Chemistry.—The effect of the injection of calcium upon the content of calcium in the blood was not constant. Whether or not results would be the same if calcium were administered to nonpregnant women, it would be difficult to predict. It increased during the first few minutes (five to thirty minutes) after injection of calcium in nineteen of 20 cases in which determinations were made both before and five to thirty minutes after such injections (Column B in Table II). The increase, however, was not proportional

the increase in uterine contractions. For two patients (No. 11 and 22 in Table III) manual rotation of the occiput from posterior to the anterior position was done, and the child was delivered by extraction with forceps. For the third patient (No. 23 in Table III), extraction of the infant with low application of forceps was done, with a moderate amount of difficulty. The infant of the fourth patient (No. 17 in Table III) was delivered by means of cesarean section because of pelvic-fetal disproportion. In none of these cases in which birth of the infant was obstructed did the administration of calcium seem to do harm.

In the remaining 16 cases of the 23 in which the administration of calcium was successful in increasing the effectiveness of uterine contractions, the patients progressed uneventfully to parturition after the injection of calcium. Of these patients, 13 were delivered within four hours and one each was delivered in five, seven, and nine hours, respectively. All but one gave birth to infants spontaneously. For the one who did not, delivery with the low application of forceps was done because of slowing of the fetal heart.

General Systemic Effects of Calcium Gluconate.—No marked systemic effect was observed after the administration of calcium. Five of the 26 patients regurgitated the gastric contents during injection

TABLE I. ADMINISTRATION OF CALCIUM GLUCONATE TO 26 PREGNANT WOMEN: DOSAGE OF DRUG AND VALUES FOR BLOOD PRESSURE, PULSE AND RESPIRATION RATES AT AND AFTER ADMINISTRATION

PATIENT	-CA. ION, MG. PER KG. BODY WEIGHT	REGURGITA- TION	BLOOD PRESSURE MM. OF HG		PULSE RATE PER MIN.		RESPIRATION, RATE PER MIN.	
			A*	B†	A*	B†	A*	B†
1	1.24	No	-	-	-	-	-	-
2	1.25	No	130/90	-	98	-	24	-
3	1.92	Yes	-	136/88	-	89	-	20
4	2.18	No	120/75	120/90	76	64	16	18
5	2.24	No	132/98	-	96	-	24	-
6	2.50	No	108/82	104/84	86	88	24	20
7	2.69	No	140/100	150/90	72	60	20	18
8	2.82	No	122/80	122/68	74	77	18	19
9	2.85	No	110/65	114/70	80	64	20	20
10	2.96	No	110/78	136/80	84	86	18	18
11	2.96	No	110/88	-	100	-	24	-
12	3.02	No	114/86	-	104	-	24	-
13	3.05	Yes	128/88	155/110	70	88	19	20
14	3.05	No	134/70	126/80	100	100	24	22
15	3.22	No	128/90	146/106	84	78	16	18
16	3.26	No	112/76	130/80	74	64	15	16
17	3.26	No	136/94	142/96	90	76	20	24
18	3.40	No	120/80	130/90	92	-	20	-
19	3.57	Yes	122/76	-	82	-	18	-
20	3.75	Yes	144/92	130/84	79	74	19	17
21	4.04	No	108/80	102/72	84	80	18	16
22	4.30	No	-	-	-	-	-	-
23	4.50	No	126/56	134/72	92	88	16	22
24	4.66	Yes	128/90	150/96	100	80	20	18
25	4.89	No	135/95	135/98	88	88	22	28
26	5.08	No	114/80	120/80	76	66	14	12

*A, At time of injection.

†B, Five minutes after injection.

TABLE III. ADMINISTRATION OF CALCIUM GLUCONATE TO TWENTY-SIX PREGNANT WOMEN: DOSAGE, VALUES FOR BLOOD CALCIUM, DILATATION OF CERVIX, PARITY OF PATIENTS AND UTERINE CONTRACTIONS RESULTING*

PA-TIENT	CERVIX DILATED TO, CM.	PAR-ITY	MG. CA. PER KG. BODY WEIGHT	BLOOD CA., MG. PER 100 C.C.		UTERINE CONTRACTIONS					
				A	RISE	FREQUENCY, MIN.		DURATION, SEC.		INTENSITY	
						A	B	A	B	A	B
1	9	4	1.24	-	-	5	1	40	60	Wk.	Str.
2	4½	1	1.25	-	-	2-3	1½-2	35	35	Wk.	Str.
3	2	1	1.92	10.4	1.8	3½	2½	45	45	Str.	Str.
4	2	0	2.18	10.8	1.0	2	2	45	45	Mod.	Str.
5	6	0	2.24	9.8	0.0	2	2	75	75	Mod.	Mod.
6	3	1	2.50	9.3	1.8	3½	3	30	40	Wk.	Mod.
7	3	1	2.69	10.6	1.0	3	3-1	30	30	Str.	Str.
8	3	1	2.82	-	-	5-10	1½	10	30	Wk.	Str.
9	4	2	2.85	8.51	0.99	3½	3½	60	60-90	Mod.	Str.
10	2	2	2.96	6.6	1.2	3	1½	30-75	60	Mod.	Str.
11	10	1	2.96	8.71	1.39	3-5	2	30	30	Mod.	Mod.
12	9	1	3.02	9.3	1.8	6-7	2½-3	45-60	30	Mod.	Str.
13	4	0	3.05	9.1	2.7	3	2	45	45	Str.	Str.
14	1	1	3.05	9.7	1.0	2½	1	75	75	Str.	Str.
15	0	1	3.22	8.6	1.0	10	5	20	20	Wk.	Mod.
16	0	1	3.26	9.5	-	3-12	4	45	60	Wk.	Mod.
17	0	0	3.26	9.5	1.4	3-6	1-1½	60-120	60-120	Str.	Str.
18	4	1	3.40	9.5	0.8	3-4	1-1½	30-80	30-60	Mod.	Str.
19	5	0	3.57	10.5	0.6	3-3½	1-1½	50	50	Mod.	Str.
20	3	1	3.75	10.4	1.0	2	1	35	60	Mod.	Str.
21	0	2	4.04	8.5	1.9	3-4	2-3	75-120	75-120	Str.	Str.
22	9	2	4.30	8.68	2.72	2-3	1½	30	30	Mod.	Mod.
23	10	0	4.50	9.3	1.6	5½	1½-3½	60	30-60	Mod.	Str.
24	3	1	4.66	-	-	5-9	1	60-120	60-75	Wk.	Str.
25	1½	0	4.89	7.5	0.8	5	3	40	40	Mod.	Mod.
26	2	2	5.08	8.51	1.39	2-10	1-2	60-120	30-120	Mod.	Mod.

*A, At time of injection. B, Five to thirty minutes after injection. Wk., weak; Mod., moderate; Str., strong.

The effect of calcium on uterine contractions was not proportional to the amount of calcium injected per kilogram of body weight, or to the actual increase in calcium in the blood after the injection of calcium. Values for calcium in the blood corresponded to those found to exist during labor by other workers,^{1, 7, 8, 20, 27-29, 33} but the value for calcium in the blood after the injection of calcium did not increase more than 2.72 mg. per 100 c.c., in contrast to greater increases observed by workers in experimental laboratories in similar studies.^{11, 12, 24, 38}

A few patients complained of a sensation of faintness and of profuse perspiration during injection of the calcium. Reductions of values for blood sugar of from 10 to 31 mg. per 100 c.c. within five to fifteen minutes by the intravenous injection of calcium salts have been reported. The sensation of faintness and complaint of profuse perspiration previously mentioned may be referable to the temporary presence of hypoglycemia. The symptoms disappeared after the injection had been completed, and in no case was it necessary to cease administration. Administration of calcium was discontinued for thirty to sixty seconds, however, as a precautionary measure.

Effect of Calcium Gluconate on Newborn Infants.—None of the babies born to these 26 mothers exhibited any ill effects referable to the administration of calcium.

TABLE II. ADMINISTRATION OF CALCIUM GLUCONATE TO 26 PREGNANT WOMEN: WEIGHT OF PATIENTS, AMOUNTS AND SOLUTIONS EMPLOYED, AND CALCIUM CONTENT OF THE BLOOD AT AND AFTER ADMINISTRATION

PATIENTS		CALCIUM GLUCONATE			BLOOD CALCIUM, MG. PER 100 C.C. OF BLOOD				
NO.	BODY WT., KG.	SOLUTION, C.C.	SOLUTION, PER CENT	CALCIUM ION, MG. PER KG. BODY WEIGHT	A†	B†	C†	INCREASE	
								ACTUAL	THEORETIC
1	58.2	4	20	1.24	-	-	-	-	1.61
2	71.8	10	10*	1.25	-	-	-	-	1.63
3	93.6	20	10	1.92	10.4	12.2	12.7	1.8	2.50
4	57.7	14	10	2.18	10.8	11.8	11.4	1.0	2.84
5	80.5	20	10	2.24	9.8	9.8	9.6	0.0	2.91
6	71.8	20	10	2.50	9.3	11.1	9.8	1.8	3.26
7	66.8	20	10	2.69	10.6	11.6	-	1.0	3.50
8	63.6	20	10	2.82	-	-	-	-	3.68
9	63.1	20	10	2.85	8.51	9.5	-	0.99	3.71
10	81.8	27	10	2.96	6.6	7.8	7.6	1.2	3.85
11	79.1	13	20	2.96	8.71	10.1	-	1.39	3.85
12	74.5	25	10	3.02	9.3	11.1	10.3	1.8	3.94
13	59.0	20	10	3.05	9.1	11.8	-	2.7	3.96
14	59.1	10	20	3.05	9.7	10.7	-	1.0	3.96
15	55.9	20	10	3.22	8.6	9.6	-	1.0	4.19
16	69.1	25	10	3.26	9.5	-	-	-	4.24
17	82.7	15	20	3.26	9.5	10.9	8.9	1.4	4.24
18	79.5	15	20	3.40	9.5	-	10.3	0.8	4.42
19	63.1	25	10	3.57	10.5	11.1	10.4	0.6	4.64
20	60.0	25	10	3.75	10.4	11.4	11.2	1.0	4.87
21	66.8	15	20	4.04	8.5	10.4	9.2	1.9	5.25
22	62.7	15	20	4.30	8.68	11.4	-	2.72	5.60
23	60.0	15	20	4.50	9.3	10.9	-	1.6	5.85
24	77.2	20	20	4.66	-	-	-	-	6.06
25	57.3	16	20	4.89	7.5	8.3	-	0.8	6.36
26	53.2	15	20	5.08	8.51	9.9	-	1.39	6.60

*Calcium-quinine.

†A, At time of injection; B, five to thirty minutes after injection; C, one to eight hours after injection.

to the amount of solution injected, or to the quantity of solution of calcium gluconate injected per kilogram of body weight. Actual increase expressed in milligrams of calcium per 100 c.c. of blood varied from 0 to 2.72 and the average increase would be slightly in excess of 1.32, based on calculation for 21 patients, and not all 26 of the series (Table II). The theoretic increase in calcium in the blood (Table II), if it were assumed that all the calcium remained in the blood stream a few minutes after the injection, would be the number of milligrams of calcium ions injected per 100 c.c. of blood. This theoretic increase in calcium in the blood was calculated by utilization of the estimated figure of 1:13³⁷ as the ratio of the volume of blood in liters to the weight of the body in kilograms. In Table II it is seen that among all 26 patients, the theoretic increase in calcium in the blood varied from 1.61 to 6.60 mg. per 100 c.c. Basis for this calculation follows:

$$\text{Mg. calcium gluconate injected} \times \frac{9 \text{ calcium ions}}{100 \text{ calcium gluconate}} = \text{Mg. calcium ions injected.}$$

$$\frac{\text{Mg. calcium ions injected}}{\text{Patient's weight in kg.}} \times \frac{13 \text{ body weight}}{1 \text{ blood volume (liters)}} = \text{Mg. calcium ions injected per liter of blood.}$$

$$\text{Mg. calcium ions injected per liter} \times \frac{1 \text{ liter}}{10 (100 \text{ c.c.})} = \text{Mg. calcium ions injected per 100 c.c. of blood.}$$

sulted from its use in such instances. Comparatively small doses of analgesic agents in the form of pentobarbital sodium or elixir of paraldehyde were administered orally to some of these patients according to the usual indications for such agents, although care was exercised not to employ the drugs until after the effect of the calcium had been established.* Five patients received no analgesic agent. Two additional patients received no analgesic agent until twenty-four to forty-eight hours had elapsed after administration of calcium. Eight patients received pentobarbital sodium before calcium was administered. Dosage for these patients varied from $1\frac{1}{2}$ gr. (0.1 Gm.) administered two minutes before injection of calcium to 6 gr. (0.4 Gm.) administered two to four hours before injection of calcium. Sixteen patients received analgesic agents after the administration of calcium. Among these were 5 patients who had received some type of analgesic agent previous to the injection of calcium. Of the 16 patients previously mentioned, 13 received analgesic agents from fifteen minutes to three hours after the injection of calcium. Pentobarbital sodium in doses of $1\frac{1}{2}$ to 6 gr. (0.1 to 0.4 Gm.) and 4 drachms each of paraldehyde and aromatic elixir, making a combined dose of 8 drachms (31.0 Gm.), were employed separately. In 2 cases administration of these agents was combined so that 3 gr. (0.2 Gm.) of pentobarbital sodium and 8 drachms (31.0 Gm.) of elixir of paraldehyde were administered. That uterine contractions which have been stimulated by the administration of calcium may slow or even cease when analgesic agents are administered soon afterward was noted in 2 of the 16 cases. It would seem prudent, therefore, to withhold analgesic agents from calcium-treated patients who have uterine inertia until definite progress has been made. If analgesic agents are administered, they must be used with the knowledge that they may defeat the purpose of the calcium.

SUMMARY AND CONCLUSIONS

A series of 26 patients in labor received solutions of calcium gluconate intravenously. After the injection of calcium gluconate the blood pressure increased slightly and the pulse rate decreased slightly, on the average. The respiratory rate was relatively unchanged. Regurgitation of gastric contents occurred in 19 per cent of cases, but it was not a troublesome feature.

On the basis of our observations it may be concluded that:

1. The administration of calcium will not relieve labor pains.
2. The administration of calcium will increase the intensity of uterine contractions and will decrease the interval between contractions but will not increase the duration of contractions. It is most useful in stimulation of the uterus in cases of inertia in the first or second stage of labor, but it cannot be expected to overcome severe dystocia.
3. The administration of analgesic agents, such as pentobarbital sodium and paraldehyde, may defeat the purpose of calcium in some cases of uterine inertia.

*The effects of the administration of analgesic agents do not appear in Tables I, II, or III.

CONTRAINDICATIONS

The chief contraindication to the intravenous administration of calcium salts is the presence in the body of drugs of the digitalis group. Digitalis and calcium exert an additive effect on the heart, as shown by Bower and Mengle and by Lieberman,²⁵ so that there is danger of the production of ventricular standstill if the two drugs are used concomitantly. Theoretically, a value for blood sugar which is already low may be further lowered to a point at which hypoglycemic symptoms will be produced in the patient. Glucose administered intravenously would in such circumstances counteract the production of these symptoms, so that the possible production of hypoglycemia is not to be considered a contraindication to the administration of calcium if the value for blood sugar is carefully maintained at normal by means of the administration of glucose. Consideration of the effects of the administration of analgesic agents to women in labor who are receiving calcium will be found in the next section of this paper.

COMMENT

It seems probable that stimulation of the uterus by the administration of calcium may be employed to good advantage clinically in cases of uterine inertia. Utilization of the effects of calcium was unsuccessful when the patient was not definitely in labor. This conclusion is in accord with Reynolds' observation that calcium does not stimulate the uterine fistula of rabbits unless the fistula has been contracting rhythmically beforehand. The pains that follow administration of the oxytocic principle of the posterior lobe of the hypophysis (pitocin) and castor oil are not to be construed as being true labor pains, unless the uterine cervix dilates and thus indicates that the pains are valid labor pains. Duration of the effect of calcium appears to be two to three hours. If the calcium has not accomplished its purpose within this time, there seems to be no reason why it should not be administered again, although this was not done in our series. Even though calcium does increase the frequency and intensity of uterine contractions, it cannot be expected to overcome the dystocia which is produced by pelvic disproportion or by improper position of the presenting part, and the fact that it does not overcome such a type of dystocia would be an advantage rather than an objection to the administration of calcium. The obstetrician need not fear that rupture of the uterus in such cases would result from overstimulation by calcium. The ideal case in which to use calcium would be one in which labor has been definitely established, in which uterine contractions are weak to moderate and occur less often than every three minutes, and in which there is no obstruction present to hinder passage of the presenting part. Dilatation of the cervix is of no moment. In such a case it could be reasonably expected that the administration of calcium would increase the frequency and intensity of uterine contractions so that labor would be terminated sooner than would be the case if calcium had not been employed. In case calcium should be used therapeutically, hard, frequent uterine contractions would render its administration unnecessary, but in our study no harm re-

THE USE OF SYNTHETIC VITAMIN E IN THE TREATMENT OF ABORTION

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INCREASING attention is steadily being focused upon the treatment of threatened and habitual abortion. This display of interest is justly warranted when one considers the importance of an uninterrupted pregnancy to the expectant mother and especially from a broader standpoint to the country, in the face of a national decreasing birth rate.

The statistical figures on abortions in general are very difficult to analyze; difficult because patients are wont to give inaccurate records, especially when criminal intent is suspected. Some observers report the incidence of abortion in pregnancy, ranging from 1 in 5¹ to 1 in 2.3.² However, among women of a fairly intelligent class, where a large majority want babies, Galloway and Paul³ report that abortion, both early and late occurred in about 8 per cent of their cases. In addition, Bishop,⁴ in a study of 7,008 pregnancies, reports 385, or 5.2 per cent, terminating in abortion. In this same series, 10.8 per cent of the women aborted at some time in their obstetric history. A recent survey, by American authors, shows that there are about 240,000 noninduced abortions in the United States each year.⁵ These figures represent a challenge to the obstetrician, which should be met with all the possible resources at his command. With these facts in mind, both the clinician and the laboratory investigator have been engaged in the search for additional information relating to the physiology, pathology, and biomechanism of spontaneous abortion. An interesting report by Huntington⁶ demonstrates that 70 per cent of the fetuses are dead or abnormal when the threatening begins. In view of such figures, the valuation of the merit of any form of therapy in the prevention of abortion is difficult. As for the causes of spontaneous miscarriages, Rock⁷ states that most spontaneous miscarriages are caused by intrinsic disturbances in the fertilized ovum, or in the maternal organism, and not by the traditional extrinsic environmental accidents to the mother. In addition, he believes that sterility and miscarriage have, in large part, a common causative factor and merely represent different degrees of diminished fertility.

The treatment of threatened and habitual abortion has passed through a series of major phases. These are, on the basis of a broad classification, complete bed rest, sedatives, endocrine therapy, and finally, vitamin therapy. Complete bed rest has not been discarded entirely as a method of treatment, for it is still being used in conjunction with the more recently advocated measures. Sedation is still being employed but primarily as an adjunct to endocrine and/or vitamin therapy. Morphine, which was formerly the most widely used sedative for this purpose, is gradually being replaced by the barbiturates. This change has come about since Dodek,⁸ and Falls, Lackner, and Krohn⁹ have demonstrated that morphine not only fails markedly to inhibit uterine contractions, but may tend to stimulate them. In addition, we are all acquainted with the relative hastening dilatation of the cervix, which frequently takes place during the first stage of labor when morphine is used, suggesting a definite stimulating effect on the uterus.

4. The administration of calcium apparently has no ill effects on newborn babies whose mothers received calcium intravenously during labor.

5. On the basis of reports in the literature, it would appear that calcium should not be administered if a drug of the digitalis group already has been administered.

6. The authors hope that the results of this investigation will stimulate additional study of the effects of the therapeutic administration of calcium during labor, so that further evaluation of the procedure as a therapeutic measure can be made.

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fed on a vitamin E deficient diet are less potent in inducing ovulation on injection into estrous rabbits than extracts made from pituitaries of normal control rabbits. In addition, it appears as if it is the luteinizing substance of the pituitary, and not the follicle-stimulating substance which is decreased or depressed by a vitamin E deficiency. To test for toxic effects,³⁴ large doses of vitamin E (alpha-tocopherol synthetic and its acetate) were given to mice, dogs, rats, and cats without any such effects being noted. Rowntree and co-workers³⁵ and Dorrance and Ciccone³⁶ fed albino rats on unrefined and crude wheat germ oil and were able to produce abdominal tumors, microscopically identified as sarcomas, which could be successfully transplanted, subcutaneously and intraperitoneally. However, further investigators, Carruthers,³⁷ Evans and Emerson,³⁸ and Halter,³⁹ could not produce sarcomas, using concentrated wheat germ oil preparations. In addition, Davidson,⁴⁰ by administering large doses of vitamin E, could inhibit, in many cases, the development of carcinoma in mice subjected to tarring, and therefore, believes in the anticarcinogenic value of wheat germ oil.

The clinical application of the above data has been reported by several observers whose findings will be briefly mentioned. Cromer⁴¹ found that vitamin E, when given early, and in sufficient dosage, had some value in cases of recurrent and threatened abortion. Watson²⁴ reported good results in habitual, previous, and threatened abortions, but found wheat germ oil without any effect in his cases of sterility. Shute⁴² found that there was a deficiency of vitamin E in his cases of spontaneous abortion, and he called attention to the value of wheat germ oil as a prophylactic and therapeutic treatment for such cases. His results were very satisfactory. Large doses of vitamin E were found to occasionally produce an idiosyncrasy in certain individuals.⁴³ In further experiments, he found no basis for apprehension that labor might go beyond term or never observed any delay in the onset of labor due to the oil.⁴⁴ Watson and Tew,²³ Currie,²¹ and Vogt-Möller,²⁰ also report very enthusiastically on the usage of vitamin E for habitual abortion. More recently, Collins and co-workers²⁵ reported the efficacy of wheat germ oil along with thyroid and progestin in combating threatened and habitual abortion, and dispelled the fear of a delivery of a malformed fetus in those cases in which abortion had been successfully treated. Blood serum studies indicating deficiency of vitamin E could not be corroborated by this group in their cases, nor could Cuthbertson and Drummond⁴⁵ demonstrate an excess of antitryptic activity in the serum in vitamin E deficient rats.

PATIENTS STUDIED

The cases studied included only private patients. Service cases were not utilized for several distinct reasons. Private patients present a more accurate history pertaining to previous pregnancies and can be depended upon to carry out instructions and report symptoms more reliably. In addition, when a woman employs a private physician for delivery, she signifies her desire of bearing a child, whereas when clinic patients are admitted to general wards, there is no way of checking criminal induction of abortion. Moreover, service patients are not as willing to divulge this evidence as are private patients.

All of the patients observed, with one exception, were hospitalized,* either at the time of threatening to abort or when ready for delivery. The one exception was a woman who aborted at home during the eleventh week of pregnancy. Another patient threatened to abort while in the hospital, following an appendectomy during the fifth month of pregnancy.

The patients were divided into three groups, as follows: habitual abortion, including those who had two or more spontaneous abortions (there were 7 in this group); previous abortion, comprising those who

*At the Prospect Heights Hospital or the Swedish Hospital in Brooklyn.

The use of endocrines in the treatment of threatened and habitual abortion has come to the fore with increasing knowledge of the control of uterine motility.

Reynolds and Allen,¹⁰ Allen and Reynolds,¹¹ and Krohn, Falls, and Lackner,⁹ and others have demonstrated the inhibitory effect of the corpus luteum hormone, progesterone, on uterine motility. It is upon this physiologic fact that this form of therapy is based. Satisfactory reports, substantiating the effectiveness of this plan of treatment, have appeared in the literature. Thus, Bishop,⁴ Gershenfeld,¹² Falls, Lackner, and Krohn,¹³ and Campbell and Sevringhaus¹⁴ have successfully used progesterone. The results of the latter two investigators were not very encouraging when used for threatened abortion. In addition, Rosenfeld¹⁵ has obtained good results by using the blood serum of pregnant women. The effective agent involved in his treatment was probably the gonadotropic hormone, which is known to be present in abundance during pregnancy. Thyroid extract has also been employed with equal success for the prevention of abortion by King and Herring.¹⁶ Kane¹⁷ has reported the combined usage of thyroid and progesterone to be effective in repeated spontaneous abortions. Two groups of investigators, Johnstone, Wiesner, and Marshall,¹⁸ and Finkler,¹⁹ have reported the successful employment of anterior pituitary-like sex hormone in the treatment of both threatened and habitual abortion.

Recently, however, vitamin E has been more widely employed, both as an adjunct to, or in place of, the endocrines as a therapeutic agent for these conditions.

Observations supporting the value of vitamin E in the prevention of abortion are to be found in the reports of Vogt-Möller,²⁰ Currie,²¹ Shute,²² Watson and Tew,²³ Watson,²⁴ and Collins, Weed, and Collins.²⁵

We, therefore, can see the relative merits of the various aforementioned means of treating threatened and habitual abortion. The different methods are worthy of application, either individually or combined. Practitioners may elect one or a group of methods which have been proved to be reasonably effective. The authors have utilized several of the foregoing agents with satisfactory results. In addition, more recently we have employed alpha-tocopherol acetate in the treatment of threatened, previous, and habitual abortion. The results of these experiences form the basis of this report.

CHEMISTRY AND PHYSIOLOGIC ACTION

Evans and Bishop,²⁶ in the course of their studies on fertility in rats, found an antisterility factor, which was called "X" and later became known as vitamin E. This factor was fat soluble and insoluble in water (Evans and Burr²⁷) and concentrates could be prepared from fairly fresh wheat germ oil, whose potency could be maintained for a period of years when kept vacuum sealed.²⁸ Emerson and others,²⁹ found that alpha-tocopherol was identical in vitamin E activity as the substance isolated from wheat germ oil, and the authors also isolated beta-tocopherol and gamma-tocopherol which they found to be only from one-half to one-fourth as active as alpha-tocopherol. In 1938, Karrer³⁰ and his associates described the synthesis of alpha-tocopherol and a graphic formula was published by Kunz³¹ in 1938. Evans and Burr²⁷ suggest that "sterility is a dietary deficiency disease which leads to the destruction of the germ cell in the male while in the female the ovary and ovulation remained unimpaired but there is a characteristic disturbance in gestation with the death and resorption of the developing young." Rat experiments showed further that vitamin E, which was necessary for development of the fetus and completion of gestation, could not be replaced by either pituitary hormone or prolan A.³² Rowlands and Singer³³ found that extracts of the pituitaries of rats

TABLE I. HABITUAL ABORTIONS

CASE	NAME	AGE	GRAV.	PARA	PREVIOUS ABORT.	PREVIOUS THERAPY	THERAPY		TOTAL DOSAGE (MG.)	TOTAL TIME (DAYS)	E.D.C.†	DATE OF DELIVERY	DURATION OF LABOR	RESULT	REMARKS
							BEGAN	ENDED							
1	S.S.	26	iii	0	(1) 14 wk. (2) 22 wk.	none WGO†	4 wk. 19 wk.	19 wk. 32 wk.	420 c.c. wheat germ oil	105	2/25/40	2/23/40	9 hr.	Live birth	Stained 1 day at 16 weeks
2	E.R.	28	vi	0	(1) Induced (2) Sp. ab.* (3) Sp. ab. 4½ mo. (4) Sp. ab. 5 mo. (5) Sp. ab. 7 mo.	none none none proges- tin WGO†	9 wk.	15 wk.	132	44	3/7/41	9/13/40		Aborted	Abortion at 15 weeks
3	B.S.	32	iv	i	(1) Sp. ab. 6½ mo. (2) Sp. ab. 2 mo. (3) Live birth	none none proges- tin	10 wk.	26 wk.	354	118	7/3/40	7/4/40	5 hr.	Live birth	Stained on several occasions

had one previous spontaneous abortion (there were 10 in this group); threatened abortion, of which there were 15. This made up the largest group. Vaginal examination was omitted in all patients until after the period of viability was reached.

METHOD

All 7 of the patients who had habitual abortions, with one exception, received 3 mg. alpha-tocopherol acetate* daily, starting with their first prenatal visit. The stages of pregnancy at which therapy was begun ranged from four to eleven weeks. The duration of therapy was from forty-four to one hundred and ninety-six days. The period of pregnancy to which treatment was continued, extended from the twentieth to the thirty-fifth week. The minimal total dosage was 132 mg. and the maximal, 561 mg. The one exception (Case 1), mentioned above, was started with wheat germ oil, prior to the availability of alpha-tocopherol acetate, and the patient received a total of 420 c.c. of the oil, after which the treatment was continued with the acetate.

The plan of treatment for the "previous" abortion group was essentially similar to that of the "habitual" group. Each patient, with one exception, received 3 mg. of alpha-tocopherol acetate daily. The earliest treatment was begun at five weeks and the latest at twelve weeks and continued up to periods of pregnancy ranging between fourteen and thirty-six and one-half weeks. The minimal total dosage was 273 mg. over a period of ninety-one days, and the maximal, 570 mg. over a period of one hundred and ninety days. The one exception (Case 8), received 276 c.c. of wheat germ oil before initiating alpha-tocopherol acetate therapy. The initial dose of alpha-tocopherol acetate for "threatened" abortion varied between 3 mg. and 48 mg. administered orally in divided doses during the first twenty-four hours after symptoms began. Following this initial period, the dosage was usually maintained at 3 mg. daily unless symptoms persisted or re-appeared. Treatment continued for from two days to one hundred and one days, depending upon the severity, duration, and return of symptoms. Bleeding, with or without pain, was regarded as indicative of threatened abortion. One patient, postappendectomy, referred to above, had pain without bleeding. She had markedly severe pain, associated with intermittent uterine contractions of moderate force during the fifth month of pregnancy. With the two exceptions referred to above, alpha-tocopherol acetate by mouth, was the only therapeutic agent in "previous" and "habitual" abortion.

In the "threatened" type, however, bed rest was employed in addition when symptoms appeared, and was continued until all bleeding or pain had disappeared for at least four days. No other therapy was employed, except in one patient, where progesterone was used, parenterally, previous to, and immediately following appendectomy during the fifth month of pregnancy. This was used because of the inadvisability of oral medication preoperatively, and the inability to take oral medication postoperatively because of vomiting. This was only used as a preventive measure. When, however, the symptoms of threatened abortion appeared eight days postoperatively, and vomiting was no longer present, the alpha-tocopherol alone was employed.

Toxic manifestations were not associated with the use of alpha-tocopherol acetate in any of the patients under observation in this study, nor were any idiosyncrasies encountered.

RESULTS

In the "threatened" abortion group, there were 15 cases in all. Two patients (Cases 25 and 32) aborted, one at eleven weeks, after two days of therapy, and the other at fourteen weeks, after ten days of therapy. There was one stillbirth (Case 27), in which case, death of the fetus occurred during a long labor with inertia uteri, and the post-mortem examination of the fetus showed pulmonary atelectasis. The remaining 12 delivered normal full-term infants. There was one cesarean section in this group (Case 19) because of cephalopelvic disproportion. In calculating

*Ephynal-3 mg. tablets supplied through the courtesy of Hoffman-LaRoche, Inc.

TABLE II. PREVIOUS ABORTION

CASE	NAME	AGE	GRAV.	PARA	PREVIOUS ABORTIONS	THERAPY		TOTAL DOSAGE (MG.)	TOTAL TIME (DAYS)	E. D. C.†	DATE OF DELIVERY	DURATION OF LABOR	RESULT	REMARKS
						BEGAN	ENDED							
8	R. S.	24	ii	0	Sp. Ab. * 11 wk.	5 WGO† 15	15 wk. 28 wk.	273	91	3/ 7/40	3/ 3/40	37 hr.	Live birth	
9	J. O.	34	ii	0	Sp. Ab. 12 wk.	9	36½ wk.	267	189	4/24/40	4/15/40	12 hr.	Live birth	
10	M. T.	29	ii	0	Sp. Ab. 9 wk.	7	26 wk.	333	111	7/ 5/40	5/19/40	4 hr.	Live birth, 24 hr.	Intestinal obstruction in mother. Progestin pre- and postoperative
11	J. S.	27	ii	0	Sp. Ab. 11 wk. Proluton therapy	6	34 wk.	570	190	7/10/40	7/15/40	6 hr.	Live birth	
12	M. W.	36	iii	i	Live birth Sp. Ab. 10 wk.	5	14 wk.	300	98	7/30/40	7/27/40	2 hr.	Live birth	Stained on 2 occasions. Placenta showed partial separation
13	E. L.	36	iii	i	Live birth Sp. Ab. 12 wk.	5	18 wk.	285	95	8/ 5/40	7/28/40	3½ hr.	Live birth	
14	I. G.	30	ii	0	Sp. Ab. 10 wk.	8	27 wk.	399	133	9/11/40	7/22/40	no labor	Live pre-mature	Cesarean section for advancing toxemia. Stained once during pregnancy
15	R. R.	28	ii	0	Sp. Ab. 12 wk.	8	32 wk.	432	164	10/ 5/40	10/ 8/40	2½ hr.	Live birth	
16	F. H.	25	iii	0	Induced Ab. 6 wk. Sp. Ab. 8 wk.	12	33 wk.	414	138	10/17/40	10/21/40	3 hr.	Still-birth	Toxemia of pregnancy. Infant died two days before labor
17	M. T.	29	ii	0	Sp. Ab. 11 wk.	6	31 wk.	528	176	12/28/40	1/ 2/41	10½ hr.	Live birth	

*Sp.Ab., Spontaneous abortion.

†WGO, Wheat germ oil.

‡E.D.C., Estimated date of confinement.

4	S. J.	31	iv	0	(1) Sp. ab., 7 wk. (2) Sp. ab., 7 wk. (3) Sp. ab., 7 wk.	none none none	8 wk. 35 wk.	561	187	6/27/40	5/31/40	7½ hr.	Live birth	Stained on two occa- sions
5	J. B.	37	v	i	(1) Live birth (2) Therapen- tic abortion (3) Sp. ab., 12 wk. (4) Sp. ab., 10 wk.	none none none	9 wk. 24 wk.	312	104				Aborted	Abortion at 20 weeks
6	R. G.	32	iv	i	(1) Live birth (2) Sp. ab., 8 wk. (3) Sp. ab., 11 wk.	none none	11 wk. 35 wk.	483	161	7/29/40	8/ 3/40	24 hr.	Live birth	
7	R. Y.	35	iv	i	(1) Live birth (2) Sp. ab., 3½ mo. (3) Sp. ab., 7 mo.	none none	8 wk. 32½ wk.	516	172	10/12/40	10/15/40	19 hr.	Live birth	

*Sp.Ab., Spontaneous abortion.

†WGO., Wheat germ oil.

‡E.D.C., Estimated date of confinement.

our statistics, we found that the drug failed to arrest the threatened abortion in two cases, while one patient delivered a stillbirth. The percentage of success is therefore 80.

Of the 7 cases of habitual abortion, 5 patients delivered normal full-term infants. There were 2 failures (Cases 2 and 5), in which cases the abortion occurred at the fifteenth and twentieth weeks, respectively. With 2 failures in this group, the percentage of success is 71.5.

Eight of our 10 patients with previous abortions delivered live infants. One failure (Case 10) was one complicated by intestinal obstruction in the mother. Thirty-six hours postoperatively, the patient delivered a thirty-four-week fetus, which died after twenty-four hours. The second failure (Case 16) was that of a late toxemia of pregnancy, in which case the infant died two days before labor began. The patient in Case 14 had a cesarean section for a progressive toxemia of pregnancy, and a live, premature infant, which survived, was delivered. In this group, the percentage of success was 80. The two deaths in the infants resulted from accidents or complications of the last trimester of pregnancy and were not related to the factors causing abortion.

DISCUSSION

The authors fully appreciate the difficulty in evaluating the therapeutic importance of any method or agent to prevent spontaneous abortion. It is recognized that spontaneous abortion, not uncommonly, threatens pregnancies, where the latter continue successfully to term without any measures having been taken to combat possible accident. It is also conceded that many habitual and previous aborters, may, without aid, carry subsequent pregnancies to successful termination. Unfortunately, reports citing accurate figures of these instances are not commonly available. However, a very recent report⁵ tends to show that after one spontaneous abortion, the expectancy that the next pregnancy will not result in an abortion is about 70 per cent; and that after 2 abortions the expectancy of no abortion in the next pregnancy is about 30 per cent. From reports of numerous observers, however, the various therapeutic agents, cited earlier in this report, appear to offer a more satisfactory opportunity for a full-term pregnancy, than is available without therapy to the type of patient under observation. Although one must be cautious in ascribing a fruitful pregnancy to any specific therapeutic measure, yet one cannot completely disregard the value of those agents, which appear to help. Thus, the various sedatives, hormones, and vitamins have earned their place in the treatment of threatened and habitual abortion. It is with a similar thought in mind that these studies were undertaken, toward the possible inclusion of an additional measure in the armamentarium of the obstetrician to combat spontaneous abortion. That this is worth while, can be attested to by the happiness of those mothers who have apparently been benefited by such efforts. The fear of abnormal babies resulting from pregnancies of successfully treated threatened abortions, is probably unfounded. Falls, Lackner, and Krohn,⁹ encountered none in their series, nor did Collins and his co-workers²⁵ referred to above. The former group, however, reported 2 abnormal fetuses in 2 of the failures that aborted. The large number of normal infants born after therapy was instituted, during their threatening attempts, are difficult to correlate with the number of abnormal fetuses reported by Huntington and referred to above. To look further perhaps into the negative side of the question, as to the

TABLE III. THREATENED ABORTION

CASE	NAME	AGE	GRAV.	PARA	PREVIOUS ABORTION	SYMPTOMS		TIME OF ONSET	TOTAL DOSAGE	TOTAL TIME	E. D. C.*	DATE OF DELIVERY	DURATION OF LABOR	RESULT	REMARKS
						PAIN	BLEED-ING								
18	Y. G.	31	i	0	0	No	Yes	10 wk.	150 mg.	50 days	3/26/40	4/ 9/40	8 hr.	Live birth	Cesarean section, syphilitic, cardiac, cephalo-pelvic disproportion
19	D. C.	34	ii	i	Stillbirth	Yes	No	22 wk.	150 mg.	50 days	12/19/40	12/17/40	11 hr.	Live birth	
20	S. M.	32	ii	i	0	Yes	Yes	9 wk.	303 mg.	101 days	4/16/40	3/31/40	4½ hr.	Live birth	Appendectomy at 20 weeks, 1 wk. postoperative painful contractions
21	L. A.	34	i	0	0	No	Yes	11 wk.	225 mg.	67 days	4/ 6/40	4/10/40	15 hr.	Live birth	
22	J. J.	26	i	0	0	Yes	No	21 wk.	84 mg.	7 days	4/12/40	4/10/40	9 hr.	Live birth	
23	L. R.	28	i	0	0	No	Yes	11 wk.	42 mg.	7 days	7/ 8/40	7/ 9/40	1¾ hr.	Live birth	Cardiac mother
24	A. D.	33	i	0	0	No	Yes	7 wk.	200 mg.	68 days	8/ 7/40	7/27/40	3 hr.	Live birth	One year sterility
25	S. B.	26	i	0	0	Yes	Yes	11 wk.	9 mg.	2 days				Aborted	
26	F. S.	34	iii	ii	0	Yes	Yes	21 wk.	27 mg.	7 days	5/19/40	6/16/40	4 hr.	Live birth	Inertia uteri. Pulmonary atelectasis in infant
27	R. E.	28	i	0	0	No	Yes	17 wk.	150 mg.	28 days	7/23/40	8/ 4/40	33 hr.	Stillbirth	
28	S. B.	29	i	0	0	No	Yes	9 wk.	159 mg.	52 days	10/24/40	10/18/40	18 hr.	Live birth	
29	S. S.	27	ii	i	0	Yes	Yes	18 wk.	150 mg.	49 days	8/30/40	8/30/40	6 hr.	Live birth	
30	B. K.	32	ii	i	0	Yes	Yes	19 wk.	135 mg.	41 days	8/31/40	9/ 6/40	12 hr.	Live birth	
31	P. T.	32	i	0	0	No	Yes	11 wk.	129 mg.	42 days	11/19/40	11/17/40	6½ hr.	Live birth	
32	B. H.	34	i	0	0	Yes	Yes	14 wk.	39 mg.	10 days				Aborted	

*E.D.C., Estimated date of confinement.

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ON THE MAGNESIUM SULFATE AND ETHER CIRCULATION TIMES DURING PREGNANCY*

A STUDY OF 300 PATIENTS

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THE last few years have witnessed great strides in the study of the physiologic changes taking place in the maternal circulation during pregnancy. One of the phases concerning which there is very little consonance of opinion is the changes in the circulation time (the inverse variant of the blood velocity). Our attention was attracted some time ago by the marked increase in blood velocity observed in a small group of pregnant women.^{1, 2} In the present study our investigation was furthered in an extensive group of pregnant women.

In 1880 Remy³ claimed that the blood velocity was increased during pregnancy. To explain the functional murmurs of pregnancy Fromme⁴ used Sahli's explanation⁵ that functional murmurs are caused by increased blood velocity. Kautsky⁶ postulated that the blood velocity is increased in pregnancy. Klee,⁷ in 1924, using the fluorescein method of Koch,⁸ found the average circulation time in pregnancy within the upper normal limits of that method (thirteen to twenty-five seconds).

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effectiveness of certain therapeutic biologic agents, we cite a few observations. Galloway and Paul³ observed 2 cases of threatened abortion where proluton led to a prompt increase in pain and bleeding followed by rapid abortion. Sevringhaus and Campbell¹⁴ report relatively little success in the treatment of threatened abortion with progestin. Young⁴⁶ further questions the effectiveness of small doses of prolan when the excretion of the hormone in a normal pregnancy reaches many thousand times the quantity employed. Caution is necessary in evaluating the effectiveness of the apparently small doses of progesterone employed with evident success. The doses theoretically are insufficient when compared with the normal excretion rate of pregnanediol cited by Venning and co-workers.⁴⁷ Dietetic influences affect the reproductive process, and lack of vitamins A and E are attended by serious interference with the intrauterine development of the fetus. The varied biologic and vitamin preparations all seem to be successful in a relatively large number of cases, and we hope that future laboratory workers will help correlate the mechanisms by which these therapeutic agents act.

SUMMARY

1. Evaluation of various prophylactic and therapeutic agents in the treatment of abortion is presented.

2. Alpha-tocopherol acetate, a synthetic vitamin E oral preparation, was used in the treatment of threatened, previous, and habitual abortion in a total of 32 cases.

3. In this series there were 15 threatened, 7 habitual, and 10 previous abortions.

4. In the threatened abortion group, 80 per cent of the patients delivered normal infants. In the previous abortion group, the percentage of success was 80, while in the habitual abortion group, the percentage of success was 71.5.

5. No abnormalities of the fetus have been observed.

CONCLUSION

Caution is necessary in evaluating the effectiveness of synthetic vitamin E in the treatment of threatened, previous, and habitual abortion. We realize that our report is based on the study of a group of cases too small in number to warrant a positive conclusion. However, we do feel that the results are sufficiently encouraging to stimulate further investigation by others.

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five second mark. The five seconds are subtracted from the circulation time that is finally recorded. The test may be repeated within a few minutes with practically duplicate results. The safety of the test has been amply demonstrated.^{1, 17} The magnesium sulfate circulation time (arm-to-tongue time) serves as an index of the functional capacity of the heart as a whole.

With the needle in situ, and after the lapse of about one minute, the ether circulation time is then determined.^{18, 19} A mixture of 5 minims of ether and 5 minims of warm normal saline previously drawn up in a tuberculin syringe are injected as rapidly as possible. The time is recorded from the moment of injection until the onset of the end-point which is the perception of ether by the patient or by the observer. Usually this is accompanied by a cough or grimace on the part of the patient. The ether test thus has the advantage of being both subjective and objective. The ether circulation time (arm-to-lung time) serves as an index of the functional capacity of the right side of the heart. The magnesium sulfate circulation time reading minus the ether circulation time reading is equivalent to the lung-to-tongue circulation time and serves as an index of the functional capacity of the left side of the heart.

RESULTS IN NORMAL PREGNANCY

1. *Magnesium Sulfate (Arm-to-Tongue) Circulation Time.*—Five hundred sixty-four determinations of the magnesium sulfate circulation time were performed in 285 normal pregnant women; 312 observations ante partum and 252 post partum (Table I). The arm-to-tongue circulation time ante partum varied between 5.5 seconds and 15.2 seconds, an average of 9.9 seconds; post partum between 6.8 seconds and 15.2 seconds, an average of 10.4 seconds. These figures may be contrasted with the range in normal nonpregnant women of 7.0 to 17.8 seconds, an average of 12.9 seconds.¹

TABLE I. MAGNESIUM SULFATE CIRCULATION TIMES IN NORMAL PREGNANCY

	PRIMIPARAS		MULTIPARAS		ENTIRE SERIES		TOTAL
	ANTE PARTUM	POST PARTUM	ANTE PARTUM	POST PARTUM	ANTE PARTUM	POST PARTUM	
No. of tests	117	93	195	159	312	252	564
Average value (Sec.)	9.5	9.7	10.1	10.7	9.9	10.4	
Range (Sec.)	5.5-15.0	6.8-12.6	7.0-15.2	7.4-15.2	5.5-15.2	6.8-15.2	
No. of patients	105		180				285

During the first four months of gestation, the arm-to-tongue circulation time shows a tendency to diminish gradually (Fig. 1, 4). It should be noted, however, that even in this uncertain period the circulation time shows a definite trend to fall below the average nonpregnant value. From the sixteenth week through the thirty-fifth week of gestation, there seems to be a definite decrease in the average arm-to-tongue circulation time, the level being fairly well maintained between 9.0 and 10.0 seconds. In the latter portion of this period (twenty-ninth to thirty-fifth week inclusive), there is a steady slope from 10.0 seconds to 9.4 seconds. In the thirty-fifth to fortieth week there begins a steady though very moderate increase in the arm-to-tongue circulation time, ranging from 9.4 seconds to 11.0 seconds. During the week preceding delivery, this higher level is maintained fairly constantly. During the first 14 post-partum days, the level of the last ante-partum week is very little changed.

So far as a comparison of primiparas (105 patients) and multiparas (180 patients) is concerned, no definite conclusion may be drawn, although the tendency of multiparas to maintain a relatively more even trend of circulation time than do primiparas must be noted. Moreover, the blood velocity is significantly more rapid in primiparas than in multiparas, both ante partum (9.5 seconds and a range of 5.5 to 15.0 seconds as compared with 10.1 seconds and a range of 7.0 to 15.2 seconds) and post partum (9.7 seconds and a range of 6.8 to 12.6 seconds as compared with 10.7 seconds and a range of 7.4 to 15.2 seconds) (Table I).

In 1933 Spitzer,⁹ using the decholin method¹⁰⁻¹² in 27 normal pregnant women, found the blood velocity within the normal limits of that method (ten to sixteen seconds, average 14.3 seconds). There was some slowing of the circulation in 4 cases of toxemia of pregnancy, in 3 cases of eclampsia, and in 1 case of mitral stenosis. In 1936 Cohen and Thomson¹³ employed the cyanide method of Robb and Weiss¹⁴ in 36 normal pregnant women. There was a decrease in the average arm-to-carotid circulation time from the seventeenth to the thirty-sixth week of pregnancy inclusive; an increase in the average circulation time (relative to the seventeenth to thirty-sixth week period) from the thirty-seventh to the fortieth week reaching a peak value at the thirty-eighth week of 15.6 seconds (which is the average value in normal nonpregnant women); and a decrease in the average circulation time following delivery which persisted until the seventh post-partum week. In 1937 Greenstein and Clahr¹⁵ published the results of 52 saccharin arm-to-tongue determinations¹⁶ in 13 normal pregnant women. Their average value varied from 10.9 seconds at the eighteenth week of gestation to 14.7 seconds at the thirty-eighth week, followed by a decrease to 13.5 seconds at the time of delivery. This progressive delay was exhibited by 10 of the 13 cases, and then only in irregular fashion.

MATERIAL

The present series comprised 300 pregnant women between the ages of 17 and 40 years. One hundred and twelve were primiparas; 188 ranged in parity from secundiparity to undeciparity. The average age of the primiparas was 23.0 years and of the multiparas 28.8 years. Both magnesium sulfate and ether circulation times were performed successively, the tests being repeated monthly on each patient when circumstances permitted; one and preferably two determinations of both circulation times were determined during the two weeks after delivery. The number of observations on the same patient varied between one and five. Special attention was paid to the week prior to delivery and the two weeks post partum.

A total of 599 magnesium sulfate and 546 ether circulation times were determined: 564 magnesium sulfate circulation times were performed on 285 normal pregnant patients, and 511 ether circulation times in 274 patients of this group; 15 magnesium sulfate and 15 ether circulation times in 6 patients with rheumatic heart disease; and 20 magnesium sulfate and 20 ether circulation times in 9 patients with toxemias of pregnancy. The duration of gestation was calculated back from the actual day of delivery, the duration of a full-term pregnancy being taken as ten lunar months or two hundred and eighty days.

TECHNIQUE

The patient reclines as nearly as possible flat in bed with the arm held at the level of the right auricle. She is informed that she will experience the sudden onset of a transient hot sensation in the pharynx and tongue which she is instructed to signal with the word "now." She is also cautioned to relax as much as possible. Five cubic^{1,2} centimeters of a warm 10 per cent aqueous solution of magnesium sulfate,* drawn up in a 10 c.c. syringe with an 18 gauge needle, are injected as rapidly as possible in a large antecubital vein. The circulation time is recorded with a stop watch from the beginning of the injection until the onset of the end point. To facilitate the test and insure accuracy when it is performed by one person unassisted, it has been our practice to start the stop watch and to begin the injection at the moment the hand of the stop watch is crossing the

*Magnesium sulfate (reagent crystals), Merck and Company, Inc., was used in this investigation.

II. Ether (Arm-to-Lung) Circulation Time.—Five hundred eleven determinations of the ether circulation time were performed on 274 normal pregnant women, 290 observations being ante partum and 221 post partum (Table II). The arm-to-lung circulation time ante partum varied between 3.0 and 9.2 seconds, an average of 5.4 seconds; post partum, between 3.2 and 8.4 seconds, an average of 5.5 seconds. The ether circulation time in normal nonpregnant women averages 5.7 seconds, with extremes of 2.6 to 10.0 seconds.¹ The ante-partum and post-partum values agree quite closely. During the first four months of pregnancy, the changes in ether circulation time follow very closely the fluctuations in the magnesium circulation time. Therefore, Fig. 1, *C* demonstrates very clearly the striking uniformity of the ether circulation time during the entire course of pregnancy.

So far as a comparison of primiparas (101 patients) and multiparas (173 patients) is concerned, again the relatively faster blood velocity of primiparas must be noted, though the differences ante partum are negligible, and post partum slightly more striking.

III. Magnesium Sulfate and Ether Circulation Times in Toxemias of Pregnancy.—In a group of 9 patients with toxemias of pregnancy, 20 magnesium sulfate circulation times were determined, 16 ante partum and 4 post partum (Fig. 2). The

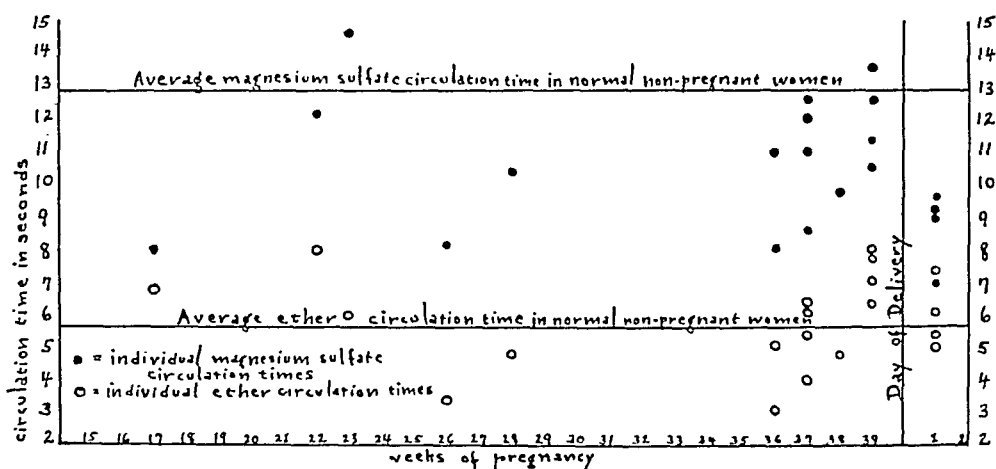


Fig. 2.—Magnesium sulfate and ether circulation times in toxemias of pregnancy.

patients were all in pre-eclamptic states with blood pressures ranging from 158 to 200 systolic and 96 to 148 diastolic. Two were primiparas and 7 multiparas, ranging in age from 19 to 39.

Practically all tests were done in the last four weeks of pregnancy. The average circulation time recorded ante partum was 10.9 seconds with extremes of 8.0 seconds and 13.6 seconds. Only 2 of the 20 readings were higher than the average value in normal nonpregnant women. The average circulation time post partum was 8.7 seconds with extremes of 7.0 seconds and 9.6 seconds.

TABLE II. ETHER CIRCULATION TIMES IN NORMAL PREGNANCY

	PRIMIPARAS		MULTIPARAS		ENTIRE SERIES		TOTAL
	ANTE PARTUM	POST PARTUM	ANTE PARTUM	POST PARTUM	ANTE PARTUM	POST PARTUM	
No. of tests	115	85	173	136	290	221	511
Average value (Sec.)	5.2	5.2	5.4	6.1	5.4	5.5	
Range (Sec.)	3.0-9.0	3.2-8.4	3.0-9.2	3.6-8.4	3.0-9.2	3.2-8.4	
No. of patients	101		173				274

Fig. 1A. Magnesium Sulfate Circulation Time in Pregnancy

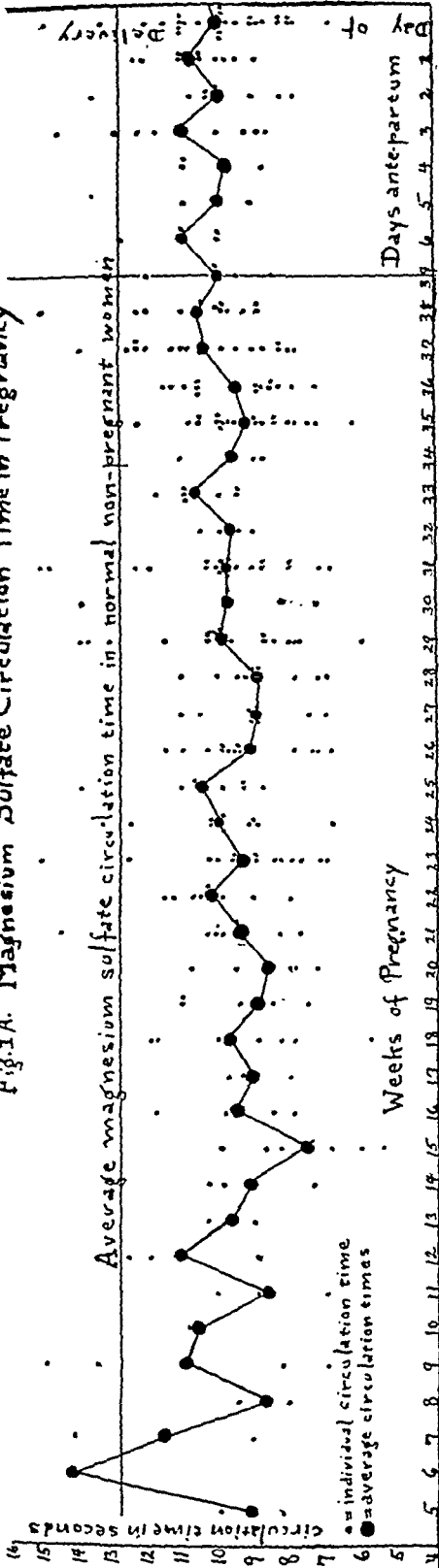


Fig. 1C. Ether Circulation Time in Pregnancy

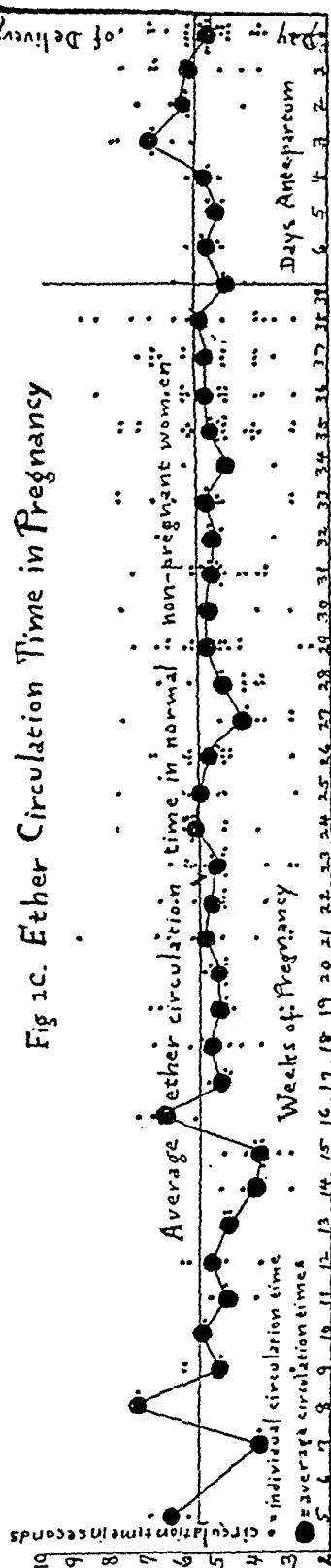


Fig. 1.

which show a tremendous increase of cardiac output far out of proportion to the rise in oxygen consumption. Such a disproportionate increase implies a diminution in the arteriovenous difference or oxygen utilization and a speeding of the circulation.

"The viscosity of the blood is decreased in pregnancy up to the sixth month, is slightly increased in the seventh month, is unknown in the latter months, and presents a consistent post-partum rise."^{13, 27} There is a steady increase from about the thirty-fifth week continuing through the post-partum period. Inasmuch as the velocity of a liquid varies inversely with its viscosity, the changes in blood viscosity may play an important role in the changes in circulation time. The analogy between blood velocity and blood viscosity, however, does not fit in with the changes in circulation time observed post partum. It must be kept in mind, however, that lactation may introduce physiologic changes that overshadow the seeming discrepancy between the blood velocity and blood viscosity changes during the puerperium.

Most studies^{28, 29} of total blood volume changes during pregnancy indicate an increase of 42 per cent³⁰ to 65 per cent³¹ closely paralleling the ante-partum changes in cardiac output. The fall in total blood volume during the last weeks of pregnancy may be an important factor in the diminution of cardiac output during that period. Moreover, as Cohen and Thomson³¹ point out, a profound disturbance in blood volume is found in endocrine conditions,^{28, 32} such as exophthalmic goiter. A possible linkage of the increase in blood volume and endocrine control is further indicated by a rather striking resemblance of the plasma volume trend with that of excretion of gonadotropic substance in normal pregnancy.³³ During pregnancy the thyroid increases in size, and there is a great deal of evidence^{34, 35} that hyperfunction of the thyroid gland may be an important factor contributing to an increase in cardiac work during pregnancy. If this be the case, the rapidity of the blood flow in pregnancy may be at least partially explained on this basis, since hyperthyroidism is the prime condition in which the blood velocity is markedly accelerated.³⁶

So far as the ether circulation time curve is concerned, the most striking feature is its similarity with the magnesium sulfate curve during the first few weeks of pregnancy. Thereafter, the ether time remains remarkably constant well into the puerperium. The implication is that during the aforementioned first trimester of pregnancy both the left and right sides of the heart share equally in the changes in the circulation; whereas from that point on, the right side of the heart remains relatively unaffected, and the left side of the heart takes the brunt of the "burden of pregnancy."

Careful study of our results demonstrates a somewhat close similarity with those obtained by Cohen and Thomson.¹³ The chief differences are: first, a much faster absolute level of the blood velocity (which is undoubtedly due to the fact that with magnesium sulfate as a circulation time agent values obtained in all sorts of normal and pathologic conditions are always faster than those obtained with the use of sodium cyanide); and second, at the thirty-eighth week of gestation their circulation time values attained the normal nonpregnant value, whereas

Sixteen ante-partum ether circulation times averaged 5.9 seconds, with extremes of 3.2 seconds and 7.8 seconds; post partum 4 circulation times averaged 6.0 seconds, with extremes of 5.0 seconds and 7.4 seconds.

IV. Magnesium Sulfate and Ether Circulation Times in Rheumatic Heart Disease.—A small group comprised 6 patients with rheumatic heart disease, ranging in age from 21 to 26 years. Five were primiparas and one a multipara. Of the primiparas, one had mitral stenosis and syphilis, 3 had mitral stenosis and regurgitation, 1 had mitral regurgitation; the multipara had mitral stenosis and regurgitation. Five patients (including the multipara) were well compensated clinically. In this group, 10 ante-partum magnesium sulfate circulation times (practically all late in pregnancy) averaged 10.8 seconds (8.0 seconds to 13.6 seconds); 4 post-partum circulation times were each 9.6 seconds. Ten corresponding ante-partum ether circulation times averaged 5.4 seconds (4.2 seconds to 7.6 seconds); 4 post-partum determinations averaged 6.7 seconds (6.6 seconds to 7.4 seconds). The sixth patient (a primipara with mitral stenosis and regurgitation who had moderate dyspnea) had a magnesium sulfate circulation time of 14.0 seconds and an ether circulation time of 9.6 seconds nine days before delivery.

ETHER REACTIONS

When Hitzig published his work on the use of ether as a circulation time agent, in 1934,³⁷ he called attention to certain ether reactions: he encountered no untoward constitutional reactions; the subject usually was aware of a "creeping" feeling along the course of the vein; 25 per cent had transient pain in this location; and 3 thromboses were noted in 28 carefully followed patients. Curiously enough, reports of ether work subsequent to Hitzig's report fail to emphasize or mention such reactions. In our series numerous reactions were encountered: 24 cases presented pain of varying intensity and duration at the site of injection; 19 had intense pain in the shoulder, 8 had pain following the course of the vein and thence, high substernally; 4 had pain along the course of the vein; 1 had pain up the arm and into the angle of the jaw; 3 had pain radiating into the axilla; 1 had almost persistent vomiting for three days; 2 had pain in the shoulder accompanied by nausea; 4 nausea; and only 2 a "creeping" feeling along the course of the vein. No thromboses were encountered. One patient developed severe pain at the site of injection for a few seconds with radiation into the shoulder and a few inches below the elbow; fifteen minutes later the hand and arm became definitely colder than the corresponding limb. This sensation lasted only a few minutes. In several patients, pain, when it developed, was of such severity as to be almost shocking. In summation, 59 reactions developed in a series of 546 ether tests, an incidence of 10.8 per cent.

DISCUSSION

The circulation time values shown through the major portion of gestation and the immediate post-partum period indicate a marked speeding of blood velocity. This marked increase is further supported by other factors. An increase in cardiac output is usually demonstrable by the third or fourth month,²⁰⁻²³ with the maximum cardiac output appearing from the sixth through the ninth lunar months. During the last four weeks of gestation (at a period when the circulation time begins to rise), the cardiac output falls^{23, 24} toward normal though not to the average nonpregnant level, and after delivery it continues its fall toward the normal level.^{20, 21, 26} Other factors remaining equal, the speed of the circulation varies directly with the cardiac output.²⁵ The changes in circulation time are, therefore, clearly linked with the changes in cardiac output.

Further corroboration of the circulation time changes is afforded by simultaneous studies of the cardiac output and oxygen consumption^{22, 23}

7. In compensated rheumatic heart disease, the magnesium sulfate and ether circulation times are within normal limits, and tend to increase with the onset of decompensation.

8. There is an incidence of 10.2 per cent of ether reactions of various types during and following ether circulation tests. The reactions include pain at the site of injection, pain along the course of the vein injected and into the shoulder, nausea and vomiting.

9. The right side of the heart is relatively unaffected during pregnancy; the left side carries the brunt of the "burden of pregnancy."

10. The changes in circulation time during pregnancy are correlated with the changes in cardiac output, oxygen utilization, blood viscosity, blood volume, and increased metabolic demands.

11. The use of ether as a circulation time agent during pregnancy apart from certain minor side reactions has no deleterious effects.

12. The use of magnesium sulfate as a circulation time agent in pregnancy is totally innocuous.

13. Any definite prolongation of either the magnesium sulfate or the ether circulation time beyond the limits established as normal for pregnancy in this work, should lead one to suspect the onset of cardiac decompensation.

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- (37) Hitzig, W. M.: *Proc. Soc. Exper. Biol. & Med.* 31: 935, 1934.
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our values still fell at least one and one-half seconds below the average nonpregnant circulation time level.

In the toxemic group, the readings were in fair accord with the values obtained in the normal group. The series is too small to permit the drawing of any conclusions. In the rheumatic heart group, the five compensated patients showed circulation times well within normal limits.³⁸ The single patient who showed incipient failure clinically had moderately prolonged circulation times relative to the values we have established as "normal" for pregnancy. This prolongation was to be expected, as the slowing of blood velocity has been shown to be roughly proportional to the degrees of cardiac failure.¹

Should the magnesium sulfate or ether circulation times be prolonged beyond the limits established herein for normal pregnancy, cardiac inadequacy should be suspected.

SUMMARY

1. Five hundred ninety-nine magnesium sulfate and 546 ether circulation times were studied in a group of 300 pregnant women, comprising 285 normal patients, 6 with rheumatic heart disease, and 9 with toxemias of pregnancy. One hundred twelve were primiparas and 188 multiparas, ranging in age from 17 to 40 years.

2. Five hundred forty-six magnesium sulfate circulation times were performed on 285 normal pregnant women. Three hundred twelve observations during the course of gestation averaged 9.9 seconds (5.5-15.2 seconds); 252 observations during the fourteen-day post-partum period averaged 10.4 seconds (6.8 to 15.2). A marked increase of blood velocity is observed throughout pregnancy and in the immediate post-partum period. During the first four months of gestation, a steady decrease in circulation time, relative to the nonpregnant level, is observed. Thereafter, until the thirty-fifth week, the circulation time remains practically constant. At this time, the circulation time increases moderately, maintaining its new level until the day of delivery and during the two weeks' post-partum period. At all times, the average magnesium sulfate circulation time remains far below the average nonpregnant level.

3. The magnesium sulfate circulation time is significantly shorter in primiparas than in multiparas, both ante partum and post partum.

4. Five hundred eleven ether circulation times were performed on 274 normal pregnant women. Two hundred ninety observations during the course of gestation averaged 5.4 seconds (3.0 to 9.2 seconds); 221 observations during the fourteen-day post-partum period averaged 5.5 seconds (3.2 to 8.4 seconds). The striking feature is that the ether circulation time is normal in value during the entire course of pregnancy and that the average circulation time is subject to practically no fluctuation.

5. The ether circulation time is slightly shorter in primiparas than in multiparas, both ante partum and post partum.

6. The magnesium sulfate and ether circulation times are normal during toxemias of pregnancy.

treatment of the menopause. Greenblatt and Torpin²⁹ have recently published a confirmation of the findings of these authors and other investigators on the amelioration of the symptoms in menopause, premenstrual tension, menometrorrhagia and hypermenorrhea with the use of androgens. However, they advised employing small doses, as many undesirable effects, such as hirsutism, enlargement of the clitoris, facial acne, and a deepening of the voice, had been reported following the use of large doses of testosterone propionate, by Loeser,³⁰ Foss,³¹ Geist, Salmon and Gaines,³² and Greenhill and Freed.³³ Israel³⁴ advocated the use of progesterone in premenstrual tension because he believed there was a corpus luteal deficiency in this syndrome.

Much of the treatment carried out by these investigators was highly empirical and the desired results were often not obtained. It was for this reason, in part, that an attempt was made to obtain some standard which would tend to suggest a more accurate therapeutic approach.

METHODS

A careful clinical evaluation of the patient, based on a thorough history, physical examination, and appropriate laboratory studies, was carried out in arriving at a differential endocrine diagnosis. A quantitative estimation of urinary prolans and estrogens was made in most cases. The prolans were assayed in a twenty-four-hour postmenstrual specimen, and the estrogens in a twenty-four-hour premenstrual specimen, in women with cyclic bleeding. In amenorrhea, a forty-eight-hour specimen of urine was used for both determinations. In the intervals in the cycle designated for collection, it was found that the respective hormones were excreted at a more constant level and in sufficient amounts to serve as some standard for evaluation of the results.

The urinary prolans were extracted by utilizing essentially the method of Katzman and Doisy.^{35, 36} A fresh refrigerated specimen of urine was precipitated with benzoic acid, and after the precipitate was removed, was again precipitated by tannic acid. The precipitates were combined and the precipitants were removed by successive washings with acetone. An aqueous solution of the precipitate was then biologically assayed in twenty-one-day-old immature female rats, according to the method of Collip, in which a unit is the minimum amount of substance which when administered subcutaneously daily for three days will produce vaginal estrus within one hundred and twenty hours. By this method, normal values for urinary prolans were found to range between 40 and 60 rat units in twenty-four hours in women between the ages of 18 and 38 years. The estrogens were removed after a two-hour acid hydrolysis of the urine, according to the method of Gallagher, Koch and Dorfman,³⁷ by continuous extraction with benzene. The solvent was subsequently removed by distillation under reduced pressure. The residue was dissolved in about 100 c.c. of ethyl ether and extracted ten times by shaking with 50 c.c. quantities of 10 per cent sodium hydroxide. About 95 per cent of the estrogenic substances were contained in the alkali. This fraction was then acidified and re-extracted with ether; the latter was removed and the residue dissolved in sesame oil, with the removal of the last traces of solvent by heat. The oil solution with the resultant estrogenic material was then biologically assayed in spayed adult female rats. A positive test was considered as reestablishment of estrus, as evidenced by the characteristic cellular changes in the vaginal smear. By this procedure normal values of 60 to 90 rat units were found to be excreted per diem in women from the ages of 18 to 38 years. Blood values for these hormones were not determined routinely because the results were not reproducible. The other laboratory examinations included a five-hour glucose tolerance test, blood calcium and phosphorus, basal metabolic rate, cholesterol, and Vollhard fluid-retention test where indicated.

The menstrual disorders encountered were divided into the following groups: hyper- and hypomenorrhea, amenorrhea (primary and secondary), dysmenorrhea, polymenorrhea, menorrhagia, metrorrhagia, and premenstrual tension. The terms as used here were essentially as defined by Fluhmann.³⁸ The endocrinopathies encoun-

AN ATTEMPT AT ENDOCRINE CORRELATION AND THERAPY IN 125 CASES OF MENSTRUAL DISORDERS

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IN A series of 125 cases, an attempt was made to demonstrate whether there was any significant relationship between menstrual disorders and endocrinopathies. For the most part therapy was aimed at correcting an existing endocrinopathy with the hope of improving the menstrual irregularity. However, it was not assumed that the presence of a menstrual disturbance implied an associated endocrinopathy, nor that an endocrinopathy predicated a menstrual disorder. Moreover, the co-existence of an endocrinopathy and a menstrual irregularity was not considered as establishing a causal relationship between the two.

Voluminous data are available, revealing that menstruation is also influenced by many extrahormonal factors, as illustrated by the presence of amenorrhea in various anemias, aortic insufficiency, tuberculosis, nutritional deficiencies, and psychic disturbances.

Within recent years, numerous articles have appeared on the endocrine control of menstruation. Roentgen therapy has been utilized by many workers¹⁻⁵ in the form of low dosage irradiation to the pituitary and ovaries in the treatment of menstrual disorders, and profound alterations in the menstrual cycle were noted attending its use. Gonadotropic hormones were employed in the control of functional uterine bleeding.⁶⁻⁸ Novak⁹ and Israel¹⁰ advocated the use of anterior pituitary-like hormones in dysmenorrhea, while others,^{5b, 11, 12} have found these preparations variously effective in the treatment of secondary amenorrhea. With the advent and use of more potent gonadotropic extracts and sex sterols, results hitherto unobtainable have been observed. Davis and Koff¹³ claim to have induced ovulation in the human being by utilizing the gonadotropic substance isolated from pregnant mare serum by Cole and Hart.¹⁴ Kennedy and Shelton¹⁵ obtained amelioration of menstrual dysfunction in a small series of cases treated with this substance. Siegler and Fein¹⁶ were able to confirm the work of these authors. Kauffman¹⁷ employed large dosages of estrogen followed by progestin to induce true menstruation, i.e. bleeding from a secretory endometrium, in castrates of even long standing. The same author¹⁸ also induced uterine bleeding in cases of secondary amenorrhea with large dosages of estrogen. Dunn¹⁹ reported on the induction of menstruation in amenorrheas of various duration by the use of anterior pituitary extracts and estrogens. It was probable that in these cases the bleeding was from a proliferative endometrium and that the estrogen was essentially responsible for the results obtained. Frank and others,²⁰ however, were unable to obtain any significant effects with even high dosages of estrogen in secondary amenorrheas. Diethylstilbestrol, an estrogenic substance synthesized by Dodds, Goldberg, Lawson and Robinson,²¹ was found to be almost as potent orally as parenterally. Many authors,²²⁻²⁴ however, have noted a rather high percentage of untoward side reactions, principally manifested by gastrointestinal disturbances, attending its use. Uterine bleeding following the withdrawal of this drug was frequently observed. Karnaky²⁵ recommended its use in high dosages in the control of functional uterine bleeding. Mocquot and Moricard²⁶ were among the first to use androgens in the treatment of gynecic disturbances. These authors, Salmon,²⁷ Shorr, Papanicolaou and Stimmel,²⁸ and others have utilized testosterone propionate beneficially in the

TABLE III. THE INCIDENCE AND RELATION OF MENSTRUAL DISORDERS TO ENDOCRINOPATHIES

DISORDER	HYPO-PITUITARY		HYPOGONAD		HYPO-THYROID		HYPER-PITUITARY		HYPER-THYROID		HYPO-ADRENIA		VIRILISM		NORMAL		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Dysmenorrhea	41	33.1* 44.5†	21	30.0 22.8	18	28.0 19.9	3	23.1 3.2	3	42.8 3.2	2	40.0 2.1	0	—	4	36.3 4.3	92	31.1* 100.0†
Oligomenorrhea	24	19.4 37.5	17	24.3 26.6	16	25.0 25.0	2	15.4 3.1	1	14.3 1.55	1	20.0 1.55	2	100.0 3.1	1	9.0 1.6	64	21.7 100.0
Hypomenorrhea	19	15.3 46.3	5	7.0 12.2	10	16.0 24.4	3	23.0 7.3	0	—	2	40.0 4.9	0	—	2	18.6 4.9	41	13.9 100.0
Premenstrual tension	12	9.6 36.4	10	14.3 30.3	6	9.1 18.2	1	7.7 3.0	1	14.3 3.0	0	—	0	—	3	27.1 9.1	33	11.1 100.0
Amenorrhea	9	7.3 37.5	11	15.7 45.8	2	3.0 8.3	1	7.7 4.2	0	—	0	—	0	—	1	9.0 4.2	24	8.1 100.0
Menorrhagia	4	3.2 23.5	3	4.3 17.8	7	10.9 41.1	2	15.4 11.8	1	14.3 5.8	0	—	0	—	0	—	17	5.7 100.0
Hypermenorrhea	5	4.0 41.7	2	2.8 16.7	4	6.4 33.3	1	7.7 8.3	0	—	0	—	0	—	0	—	12	4.1 100.0
Polymenorrhea	4	3.2 66.6	1	1.6 16.7	1	1.6 16.7	0	—	0	—	0	—	0	—	0	—	6	2.0 100.0
Metrorrhagia	2	1.7 66.7	0	—	0	—	0	—	1	14.3 33.3	0	—	0	—	0	—	3	1.0 100.0
Normal	4	3.2 100.0	0	—	0	—	0	—	0	—	0	—	0	—	0	—	4	1.3 100.0
Total	124	100.0 41.8	70	100.0 23.6	64	100.0 21.6	13	100.0 4.4	7	100.0 2.4	5	100.0 1.8	2	100.0 0.7	11	100.0 3.7	296	100.0 100.0

*Upper figures represent incidence of endocrinopathies in menstrual disorders.

†Lower figures represent incidence of menstrual disorders in endocrinopathies.

tered were classified as follows: hypopituitarism, hypogonadism, hypothyroidism, hyperpituitarism, hyperthyroidism, hypoadrenia, and virilism. The diagnosis was based on the characteristic findings in the history, symptomatology, and laboratory examinations.

RESULTS

In this series of 125 cases, 120, or 96 per cent, exhibited endocrinopathies, and there was an incidence of 1.7 menstrual disorders per patient, or 215 menstrual irregularities. This high percentage was encountered, first, because the patients were referred primarily as endocrine cases, and second, because borderline cases of menstrual and endocrine disturbances were included. However, the high incidence of menstrual disorders in this series indicated that the hormonal control of menstruation was etiologically important.

TABLE I. INCIDENCE OF MENSTRUAL DISORDERS

DISORDER	NO. CASES	RELATIVE INCIDENCE	INCIDENCE IN PATIENTS
Dysmenorrhea	65	30.0%	52.0%
Oligomenorrhea	44	20.0%	35.0%
Hypomenorrhea	32	15.0%	25.0%
Premenstrual tension	24	11.2%	19.2%
Amenorrhea	19	8.9%	15.2%
Menorrhagia	11	5.3%	8.8%
Hypermenorrhea	10	4.7%	8.0%
Polymenorrhea	6	2.9%	4.8%
Metrorrhagia	4	2.0%	1.6%
Totals	215	100.0%	169.6%

The most common menstrual disorder encountered was dysmenorrhea, with an incidence of 52 per cent (Table I). In these 65 cases of dysmenorrhea, about one-third were associated with a pelvic abnormality; O'Donel Browne³⁹ reported about 75 per cent of the cases of dysmenorrhea he observed which were explainable on a basis of a pelvic abnormality. Brown⁴⁰ in 31,309 cases found an incidence of 45 per cent of dysmenorrhea. Oligomenorrhea, with an incidence of 35 per cent, was the second most frequent menstrual disturbance found (Table I). Infantile uteri were noted in over half of these patients. The incidence of hypomenorrhea was 25 per cent (Table I). Infantile uteri also were frequently found in this group. Of less frequency was the occurrence of premenstrual tension, amenorrhea, menorrhagia, and metrorrhagia, all of which represented only about 38 per cent of the total menstrual irregularities observed, or about one-fourth. The occurrence of 169.6 per cent instances of menstrual disorders in this group was due to the existence of more than one menstrual disorder in the majority of the cases.

Of the 120 patients presenting endocrine stigmas, 160 endocrinopathies were exhibited (Table II). Hypopituitarism, which was by far the most frequently encountered condition, showed the same relative incidence of menstrual disturbances as observed in the group as a whole (Table III). In hypogonadism, amenorrhea

TABLE II. INCIDENCE OF ENDOCRINOPATHIES

DIAGNOSIS	NO. CASES	RELATIVE INCIDENCE	INCIDENCE IN PATIENTS
Hypopituitary	70	43.8%	58.3%
Hypogonad	37	23.1%	30.8%
Hypothyroid	36	22.5%	30.0%
Hyperpituitary	7	4.4%	5.8%
Hyperthyroid	4	2.5%	3.3%
Hypoadrenia	3	1.85	2.3%
Virilism	3	1.85	2.3%
Totals	160	100.00	132.8

Of this entire series of 125 patients, 63, or 50 per cent, were obese (Table IV). The obesity was most prevalent in those patients with dysmenorrhea, oligomenorrhea, and hypomenorrhea (almost 75 per cent). Sixty-two of these 63 cases of obesity, or 98 per cent, were associated with endocrinopathies (Table V), of which 50 per cent were hypopituitary, 30 per cent hypothyroid, and 13 per cent hypogonad. Fluid retention was considered significant if there was more than 25 per cent retained in the four-hour test. Forty per cent of the hypopituitary cases, 50 per cent of the hypothyroid cases, and 33 per cent of the hypogonad cases had water retention. Forty-three per cent of the cases of dysmenorrhea, 53 per cent of the cases of oligomenorrhea, 31 per cent of the cases of hypomenorrhea, 55 per cent of the cases of premenstrual tension, and 100 per cent of the cases of hypermenorrhea had fluid retention.

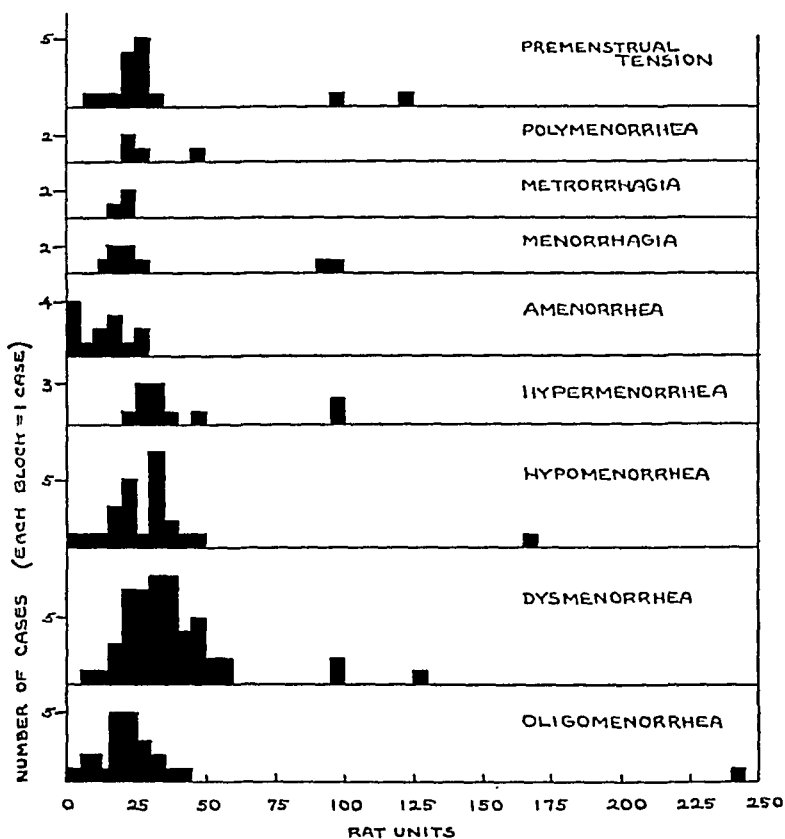


Fig. 3.—Urinary excretion of prolactin in menstrual disorders.

There was a correlative trend between increased estrogen excretion and excessive bleeding. Mean values of estrogen excretion varied from 160 rat units in menorrhagia to over 200 rat units in metrorrhagia (Fig. 2); whereas in amenorrhea, oligomenorrhea, and hypomenorrhea, there was a marked diminution in the estrogen output, with values of 20 rat units or less (Fig. 1). In amenorrhea there was a marked reduction in the excretion of urinary prolans. A diminution in urinary prolactin was also observed in dysmenorrhea, oligomenorrhea, hypomenorrhea, and less significantly in menorrhagia and metrorrhagia (Fig. 3). Similarly, a reduction of urinary prolans was observed in the cases of hypopituitarism, hypogonadism, and hypothyroidism, which corresponded with the assays encountered in the menstrual disorders most common to these groups. There was a diminution in urinary estrogens in the cases of hypopituitarism and hypogonadism.

TREATMENT

Where possible, treatment was aimed at re-establishing a normal level of endocrine function by attempting to stimulate the deficient gland.

and premenstrual tension were more frequently found. In the cases of hypothyroidism there was an increased incidence of menorrhagia. Of the remaining endocrinopathies and nonendocrine cases, there were too few patients to justify any conclusion.

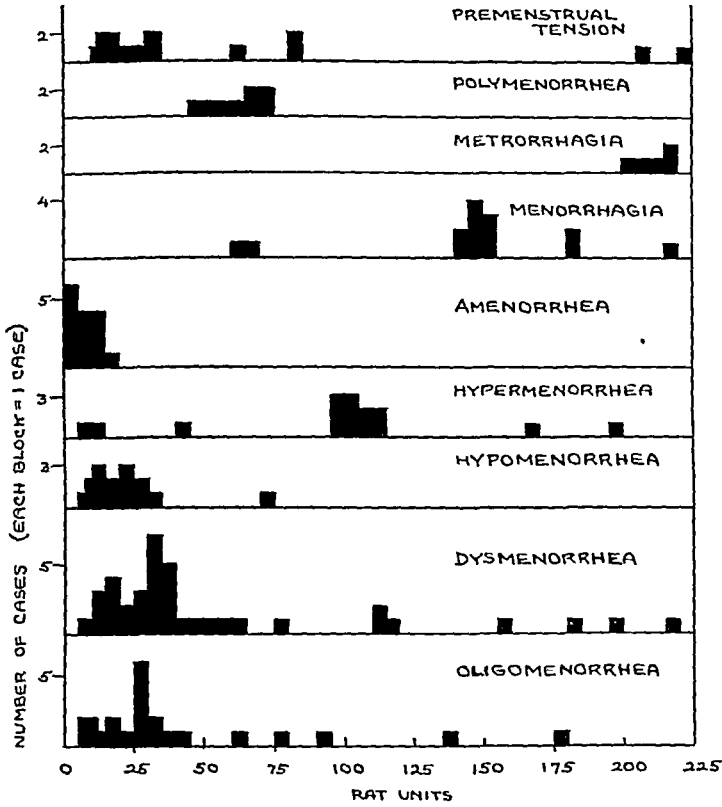


Fig. 1.—Urinary excretion of estrogens in menstrual disorders.

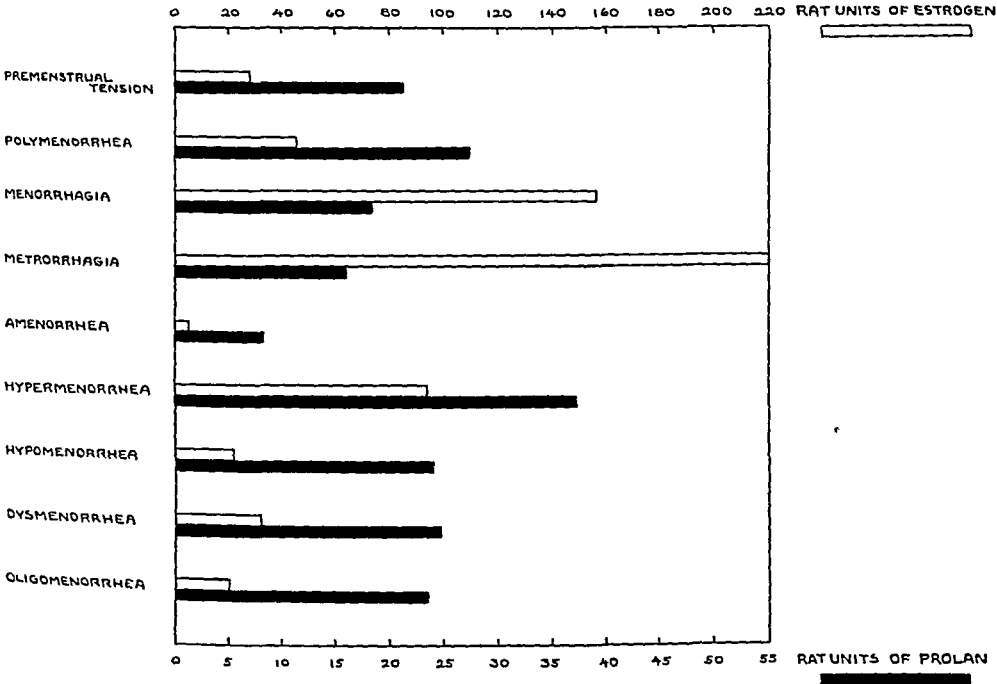


Fig. 2.—Mean rates of urinary prolactin and estrogen excretion in menstrual disorders.

for more than three cycles without interruption, because not infrequently, even though no amelioration of symptoms was observed during the course of therapy, on its withdrawal, an improvement would be noted.

In secondary amenorrhea (nonclimacteric) if the uterus was small, a preliminary course of estrogen therapy as suggested above was carried out, followed after five days by 5 mg. of progesterone every other day for four to six injections. This often resulted in bleeding from a secretory endometrium or a true menstruation. If the amenorrhea was of long standing, it was usually necessary to give more intensive estrogen therapy to stimulate uterine growth. Following bleeding, postmenstrual anterior pituitary gonadotropic hormone and chorionic gonadotropic hormones were administered as outlined above. Often, after several months of postmenstrual therapy, the uterus might again become small, necessitating further priming with estrogenic substances. In those cases where the uterus was of normal size, treatment consisted of administering 600 rat units of anterior pituitary gonadotropic hormone every other day for one to two weeks, followed by 500 rat units chorionic gonadotropic hormone every other day for one to two weeks. This was followed by one week without therapy. At the end of this week, if menses had not ensued, the same therapy was repeated. Subsequently it was found that it was more advantageous to administer the anterior pituitary gonadotropic hormone and chorionic gonadotropic hormones in combination instead of successive intervals. After menses was established, the usual regimen of postmenstrual combination anterior pituitary gonadotropic hormone and chorionic gonadotropic hormone up to the fourteenth day was carried out.

In menorrhagia where an excess of estrogen was usually excreted, treatment was designed to inhibit the excess of this hormone. This was accomplished by either administering progesterone premenstrually, starting about five to seven days before the expected period and giving 5 to 10 mg. a day, or utilizing the same principle by administering progressively increasing doses of chorionic gonadotropic hormone five to seven days before the expected period; e.g., 100 rat units (Collip) the first day, 200 R.U. the second day, 300 R.U. the third day, 400 R.U. the fourth day, 500 R.U. the fifth day, etc., giving the last injection on the first day of the period. Attempts to accomplish this same result with androgens were equally effective, but resulted in undesirable side actions. The value of utilizing large dosages of estrogen in cases of excessive bleeding as advocated by some authors²⁵ is probably based on its inhibitory effect on the pituitary and ovary. In those cases where the menorrhagia was associated with hypothyroidism, the use of thyroid in increasing doses as tolerated was employed daily intermenstrually.

In hypermenorrhea, the treatment is similar to that employed in menorrhagia. However, in addition, therapy consisting of 500 R.U. of chorionic gonadotropic hormone was administered every other day until the fourteenth day of the cycle, starting with the third or fourth day, while menstruation was still taking place.

TABLE IV. OBESITY IN MENSTRUAL DISORDERS

DIAGNOSIS	NO. OF CASES	INCIDENCE	RELATIVE INCIDENCE	INCIDENCE IN PATIENTS
Hypomenorrhea	There was more than one men- strual dis- order in some of the patients ↓	16	18.2%	12.8%
Hypermenorrhea		4	4.6%	3.2%
Oligomenorrhea		20	22.7%	16.0%
Amenorrhea		6	6.8%	4.8%
Polymenorrhea		1	1.1%	0.8%
Menorrhagia		4	4.6%	3.2%
Metrorrhagia		1	1.1%	0.8%
Dysmenorrhea		29	32.9%	23.2%
Premenstrual tension	↓	7	8.0%	5.6%
Totals	63	88	100.0%	70.4%

TABLE V. OBESITY IN ENDOCRINOPATHIES

DIAGNOSIS	NO. CASES	INCIDENCE	RELATIVE INCIDENCE	INCIDENCE IN PATIENTS
Hypopituitary	There was more than one endo- crinopathy in some of the patients ↓	39	50.7%	32.3%
Hyperpituitary		4	5.2%	3.3%
Hypothyroid		23	30.0%	19.3%
Hyperthyroid		—	—	—
Hypogonad		10	13.0%	8.3%
Hypoadrenia		—	—	—
Virilism	↓	1	1.1%	0.8%
Totals	62	77	100.0%	64.0%

In most cases where a pelvic abnormality existed, surgical or mechanical correction was initially attempted. The success of this corrective procedure was noted so that the improvement would not be attributed to other forms of therapy. In patients with cyclic bleeding where there was a diminution in estrin and prolan, as encountered in dysmenorrhea, oligomenorrhea, hypomenorrhea, and premenstrual tension, therapy consisted of, first, a preliminary course of estrogen if the uterus was infantile, in an attempt to promote uterine growth. In most instances this could be accomplished by the administration of 10,000 rat units of a-estradiol benzoate or 1 mg. dipropionate intramuscularly twice a week for two to four weeks, as guided by pelvic examination. Second, when the uterus had attained approximately normal size, the estrogen treatment was interrupted and was usually followed in a few days by withdrawal-uterine bleeding. Five days after the last injection, if there was no bleeding, and immediately after the cessation of flow if there was bleeding, or in patients with normal uteri, therapy consisting of 300 rat units (Collip) of anterior pituitary gonadotropic hormone (A.P.) and 500 rat units (Collip) of chorionic gonadotropic hormone (A.P.L.) mixed in the same syringe was administered every other day until the fourteenth day of the cycle. Half of this dose was administered daily in a group of patients during the same period of time, with the hope of producing a more physiologic rate of absorption, but no added benefit was observed. This treatment was repeated for two subsequent cycles postmenstrually. As soon as improvement was noted, treatment was withdrawn and the patient was observed to determine how long she remained free of symptoms. This type of treatment was not carried out

CASE 4.—Mrs. E. B. (amenorrhea), aged 17 years, menarche at 16 years, had 3 normal periods at thirty-day intervals with four-day flow. After appendectomy she became amenorrheic for nine months. She was a hypopituitary-hypogonad with an infantile uterus.

Assays: (48-hour specimen) 5 R.U. of prolactin, 10 R.U. of estrogen.

Therapy: Consisted of 10,000 R.U. of estradiol benzoate three times a week for two weeks. Nineteen days after onset of treatment uterus was normal size. She then received 200 R.U. of chorionic gonadotropic hormone and 300 R.U. of anterior pituitary gonadotropic hormone every other day for three weeks. Ten days after the last injection bleeding began; the flow lasted four days. She was then given 200 R.U. of chorionic gonadotropic hormone and 300 R.U. of anterior pituitary gonadotropic hormone every other day until the fourteenth day. She had another normal period forty days after the last. Therapy was repeated and the period was delayed; patient was found to be pregnant. She went to term and pursued an uneventful course.

CASE 5.—Miss I. B. (menorrhagia), aged 25 years, menarche at 12 years, twenty-eight-day cycle, seven- to eight-day profuse flow preceded by severe migraine, hypothyroid. Basal metabolic rate was minus 19; water retention, 32 per cent.

Assays: 90 R.U. of prolactin, 160 R.U. of estrogen.

Therapy: She was given 1 gr. of thyroid t.i.d. with some reduction in flow but had persistent headaches. She was then given 100 R.U. of pregnancy urine extract (P-D) on the twenty-fourth day, 200 R.U. on the twenty-fifth day, 300 R.U. on the twenty-sixth day, 400 R.U. on the twenty-seventh day, and 500 R.U. on the first day of menses. There was a marked reduction in flow and no headaches. She was given 1 gr. of thyroid t.i.d. postmenstrually until the fourteenth day and pregnancy urine extract as previously from the twenty-fourth day of the cycle, for three cycles. After ten months without therapy, the flow is normal and there have been no headaches.

CASE 6.—Miss M. S. (polymenorrhea), aged 16 years, menarche at 13 years, twenty-one-day cycle, seven-day good flow with severe dysmenorrhea which was improving spontaneously. Hypopituitary infantilism. Pelvic examination was unsatisfactory. Basal metabolic rate was minus 2; glucose tolerance test, C.B.C.; and urine normal. Cholesterol 182 mg.

Assays: 20 R.U. of prolactin, 35 R.U. of estrogen.

Therapy: 200 R.U. of chorionic gonadotropic hormone and 300 R.U. of anterior pituitary gonadotropic hormone until fourteenth day of cycle. This was followed by three periods at thirty-two- to thirty-five-day intervals with a five-day good flow and one to two days of staining with no dysmenorrhea. For six months without therapy the cycle has been thirty to thirty-two days with a five-day flow.

DISCUSSION

In a large series of cases referred to this clinic for endocrine study, 125 patients complaining of various menstrual irregularities were analyzed for the purpose of demonstrating a possible relationship between the endocrinopathy, if present, and the menstrual disturbance. The incidence of endocrine stigmas was, therefore, exceedingly high, occurring in 96 per cent of the cases. Attempts to correlate the association of a specific menstrual disorder with a specific endocrinopathy, and vice versa, revealed a significant relationship (Table III). In the majority of instances, dysmenorrhea, oligomenorrhea, hypomenorrhea, and premenstrual tension were most prevalent in hypopituitary cases. Amenorrhea was encountered most frequently in hypogonadal cases. Menorrhagia predominated in hypothyroidism, while hypermenorrhea, polymenorrhea, and metrorrhagia occurred most often in hypopituitarism, but the relationship was less significant because of the small number of patients. The chief menstrual complaints in most of the endo-

In polymenorrhea, 500 R.U. of chorionic gonadotropic hormone was administered every other day until the fourteenth day of the cycle, starting at the third or fourth day. In those patients in whom bleeding took place between the fourteenth and the twenty-fourth day, the chorionic gonadotropic hormone was administered throughout the entire cycle. When the cycle had been prolonged in this manner, the drug was again administered in the same dose postmenstrually during the fourth to the fourteenth day, to prolong the life of the corpus luteum.

In metrorrhagia, most of the patients manifested uterine and ovarian pathology and responded to surgical intervention. In the remaining patients, chorionic gonadotropic hormone therapy was administered throughout the cycle.

CASE REPORTS

CASE 1.—Miss S. B. (dysmenorrhea), aged 16 years, menarche at 13 years, cycle three to four months, interrupted flow for four days. Two years ago dysmenorrhea became more severe with lancinating pain in lumbosacral region for one week premenstrually.

Pelvic examination was normal, basal metabolic rate, plus 2; water retention, 42 per cent.

Assay: 12 R.U. of estrogen.

Therapy: 200 R.U. of chorionic gonadotropic hormone and 300 R.U. of anterior pituitary gonadotropic hormone every other day from the fifth to the fourteenth day of the cycle. She menstruated on the thirtieth day, good flow, less pain. The same treatment was repeated following the period. She menstruated twenty-eight days later with no pain, four-day flow. She was treated similarly for third cycle, followed by a period twenty-one days later with no pain. She has had no therapy for 6 months, has a twenty-eight-day cycle, four-day flow, and no pain.

CASE 2.—Mrs. B. O. (oligomenorrhea), aged 23 years, menarche at 14 years, forty- to ninety-day cycle, two-day scant flow (hypomenorrhea), was hypogonad with infantile uterus.

Assays: 20 R.U. of prolan, 12 R.U. of estrogen per diem.

Therapy: She was given 10,000 R.U. of estradiol dipropionate twice a week for two weeks. Two days after cessation of treatment, she had a four-day good flow. Postmenstrually she received 300 R.U. of anterior pituitary every other day until fourteenth day of cycle. At thirty-five days there was still no flow; uterus had regressed. She was given 20,000 R.U. of estrogen in two injections. Menses followed. Then she received 300 R.U. of anterior pituitary and 200 R.U. of chorionic gonadotropic hormone until fourteenth day. Bleeding occurred on thirtieth day. The latter treatment was repeated after cessation of flow, and next period occurred on thirty-second day. After no treatment for two months, period again became delayed. Postmenstrual anterior pituitary and chorionic gonadotropic hormones in the same dosage as previously, resulted in a period thirty-one days later. The treatment was repeated the following month and menses started on twenty-ninth day. She has had no therapy for five months during which time menses occurred twenty-eight to thirty-one days with good flow.

CASE 3.—Mrs. H. S. (hypomenorrhea), aged 30 years, menarche at 13 years, twenty-eight- to twenty-nine-day cycle, twenty-four-hour scant flow with premenstrual breast engorgement, a hypopituitary-hypogonad with an infantile uterus.

Assays: 20 R.U. of prolan, 15 R.U. of estrogen.

Therapy: She was given 10,000 R.U. of estradiol benzoate twice a week for two weeks premenstrually. Postmenstrually she received 200 R.U. of chorionic gonadotropic hormone and 300 R.U. of anterior pituitary gonadotropic hormone until the fourteenth day of the cycle for 6 cycles. Her cycle is the same and she has a three- to five-day good flow. Her uterus has remained normal in size and the flow is normal after seven months without therapy.

oligomenorrhea, and hypomenorrhea, which constituted the major types encountered, over 50 per cent are still free of symptoms, even after cessation of treatment (Table VI).

SUMMARY

1. One hundred and twenty-five cases of menstrual disorders were presented.

2. These were referred primarily as endocrine cases and were studied and treated on this basis.

3. In this group a significant correlation was found to exist between menstrual irregularities and endocrinopathies.

4. Endocrine therapy resulted in marked improvement in over 50 per cent of the patients treated.

Our appreciation is extended to Dr. W. H. Stoner of Schering Corporation, Bloomfield, N. J., for his generous supply of estradiolbenzoate (progynon-B) and progesterone (poluton), estradiol dipropionate (progynon, D. P.), pregnant mare's serum (anteron).

The chorionic gonadotropic hormone (A. P. L.) and the anterior pituitary gonadotropic hormone (Gonadotropic Factor) used in these experiments were manufactured by Ayerst, McKenna & Harrison (United States), Ltd.

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crinopathies were dysmenorrhea, oligomenorrhea, hypomenorrhea, premenstrual tension, and amenorrhea in the order named; this group constituting about 85 per cent of the menstrual disturbances. It was not the intention of this paper to attribute an underlying endocrinopathy as a cause for all menstrual irregularities, for the data were collected on the basis of the endocrinopathy and not the menstrual disorder. However, the exceedingly high incidence of menstrual disorders in patients with endocrine stigmas was considered more than a coincidence. It may well be that the presence of an endocrinopathy predisposes a menstrual disturbance. Additional data which are being accumulated may lend strength to this supposition. Data tabulated on patients worked up in a gynecology clinic from an endocrine viewpoint would do much to bring the loose ends of this problem together.

The hormone assay was found to be of considerable value in the diagnosis and treatment of these menstrual irregularities, particularly when correlated with the other laboratory procedures.

In the majority of cases, the patients were treated on the basis of the endocrine findings. Only five types of drugs were necessary to carry out optimal treatment in most cases. These were as follows: (1) Prolan A, in which the source was either anterior pituitary gonadotropic hormone or pregnant mare's serum; (2) prolan B, in which chorionic gonadotropic hormone was employed; (3) estrogenic hormone, which was utilized chiefly as estradiol benzoate or estradiol dipropionate, (4) corpus luteum extract in the form of progesterone; and (5) thyroid hormone prescribed in the form of desiccated thyroid gland substance.

TABLE VI. RESULTS OF TREATED CASES

DIAGNOSIS	NO. OF CASES	DURATION OF TREATMENT		TIME OF RESPONSE		EXTENT OF IMPROVEMENT				FAILURE		STILL IMPROVED WITHOUT THERAPY	
		MO.	AVER.	MO.	AVER.	MARKED		SLIGHT		NO.	%	NO.	%
						NO.	%	NO.	%				
Dysmenorrhea	33	1-12	3.7	1-3	2.9	27	66.6	5	15.2	6	18.2	18	54.5
Oligomenorrhea	19	1-12	4.4	1-4	3.1	13	68.4	1	5.3	5	26.3	10	53.0
Hypomenorrhea	17	1-7	3.7	1-4	2.2	12	71.0	2	12.0	3	17.0	9	53.0
Premenstrual tension	22	3-9	3.5	1-4	2.0	14	63.6	3	13.6	5	22.8	5	23.0
Amenorrhea	9	2-12	4.5	1-6	3.8	7	77.7	2	22.3	0	0	8	89.0
Menorrhagia	2	1-3	2.0	1-2	1.6	2	100	0	0	0	0	2	100
Hypermenorrhea	5	1-4	3.2	1-3	2.8	4	80.0	0	0	1	20.0	4	80.0
Polymenorrhea	3	1-5	3.0	1-3	2.5	3	100	0	0	0	0	3	100
Metrorrhagia	2	1-4	2.5	1-3	2.0	2	100	0	0	0	0	2	100
Totals	112					79	70.5	13	11.6	20	18.1	61	54.4

Utilizing treatment based on correcting the existing endocrinopathy, it was found that over 50 per cent of the patients with menstrual disturbances (Table VI) were free of symptoms even after treatment was withdrawn, although it is possible that some of these patients may yet have a recurrence. Only 18.1 per cent of the patients treated in this manner failed to respond at all, and 70 per cent of the patients improved markedly with the elimination of the menstrual irregularity, although about 16 per cent of these subsequently relapsed. In dysmenorrhea,

the ovaries,^{49, 53, 60, 61, 70} as well as growth of the clitoris and preputial glands.⁶¹ Continued administration of testosterone, however, results in eventual atrophy of the ovaries.^{45, 47} As regards the action of testosterone on the pituitary, there is evidence to suggest that, in adult female rats, testosterone inhibits,^{2, 52, 73} whereas, in immature rats, it stimulates^{49, 60, 61} the gonadotropic activity of the hypophysis. Furthermore, menstruation has been delayed and ovulation inhibited in monkeys^{30, 76} and rabbits¹² with testosterone. It appears, therefore, that when administered to female animals, testosterone exhibits a variety of properties, evoking gynecogenic and androgenic responses, the relative intensity of the component effects varying with the species and the age of the animal and the dosage and duration of the hormone administration. It would, therefore, hardly seem justifiable to base the rationale for the use of testosterone, as a therapeutic agent in women, upon a single one of its biologic properties (viz., the ability to suppress the vaginal cornification reaction in rats and mice) and ignore the other properties which biologically can be considered as antithetical and could, therefore, quite logically permit of diametrically opposite conclusions. It seems to us to be both illogical and unnecessary to seek, in animal experiments, a rationale for the use of androgens in the treatment of abnormal uterine bleeding, when a physiologic basis for their use can be found in the biologic effect which testosterone evokes in human females. Thus it has been shown that testosterone propionate, if given in sufficient amounts to woman, inhibits the secretion of gonadotropic hormone by the hypophysis,⁶² suppresses ovulation²⁴ and menstruation^{21, 25, 40, 55, 56} and abolishes temporarily the normal proliferative and secretory phenomena of the endometrium, reducing the latter to a state of involution.^{21, 25, 63} In cyclical women, in contrast to rodents, the action of testosterone propionate appears to be monophasic, viz., antigynecogenic. It was felt, therefore, since testosterone inhibits both the gonadotropic activity of the pituitary (which appears to be the primary factor in the cycle of events which culminates in uterine bleeding) and the endometrium (which is the end organ involved in the bleeding process) that possibly abnormal uterine bleeding could be controlled by utilizing this antigynecogenic property of testosterone.

Here we wish to present: (a) our experience (extending over a period of over three years) with 61 cases of abnormal uterine bleeding treated with testosterone propionate; (b) recommendations as to the optimal dosage; (c) safeguards to be employed in order to avoid the masculinization phenomena; (d) some theoretical concepts in regard to the etiology of functional bleeding and the physiologic role of androgens in the sex hormone organization of the human female; and (e) a preliminary report on the value of methyl testosterone, ethinyl testosterone and androgen implantation.

LITERATURE

In 1938, Loeser⁴⁰ reported good results in a series of 10 cases of menorrhagia treated with testosterone propionate. Five of these were apparently functional and 5 had small fibroids. The dose used varied from 500 to 1,500 mg., given during three to four weeks. Unfortunately, the author did not state what the results were

THE TREATMENT OF ABNORMAL UTERINE BLEEDING WITH ANDROGENS

THERAPEUTIC EVALUATION OF TESTOSTERONE PROPIONATE, METHYL TESTOSTERONE, ETHINYL TESTOSTERONE AND ANDROGEN IMPLANTATION

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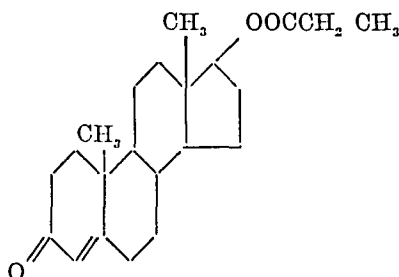
(From the Gynecological Service and the Laboratories of the Mount Sinai Hospital)

DURING the past three years, several enthusiastic reports have appeared on the use of synthetic male hormone (testosterone propionate) in the treatment of functional bleeding. To those who are interested in the problem of abnormal uterine bleeding and have been following the literature dealing with this subject, these reports sound an encouraging and welcome note. For, in spite of numerous clinical, morphologic, and hormonal studies performed in the past ten years, both the etiology and therapy of functional uterine bleeding still remain unsolved problems. A variety of theories and therapeutic agents have been in vogue at various times, but none has withstood critical analysis. It is, therefore, of considerable practical, as well as theoretical, importance to examine, critically, the results obtained with testosterone propionate.

It does not fall within the province of this paper to review and attempt to correlate the vast literature dealing with the biologic effects of androgens in laboratory animals. It is worthy of note, however, that the use of testosterone propionate as a therapeutic agent in gynecology is generally based on the observation that testosterone suppresses the vaginal (estrus) smear reaction in rats and mice.^{7, 31, 57, 72} Several authors have concluded therefrom that androgens are antagonists of the estrogens. What apparently has been overlooked is that, during the period of (testosterone induced) estrus suppression, the vaginal mucosa is markedly mucinified; that the endometrium at the same time reveals proliferative and, in some cases, progestational changes; and that the muscular coats of the uterus and vagina are hypertrophied.^{15, 38, 39, 50, 51} So that the "antagonism" between estrogens and androgens, upon which the therapeutic use of testosterone in women is based, is actually confined to one phase of the estrogen action in rodents viz., the cornification of the vaginal mucosa. In other respects, however, testosterone either simulates, complements, or augments the action of the estrogens. It is interesting to note that, in immature female rats and mice, testosterone exhibits both gynecogenic* and androgenic properties. Thus it causes premature opening and cornification of the vagina⁴¹ and hypertrophy of the uterus, in addition to follicle growth and corpora lutea formation in

*The term "gynecogen" refers to the female sex hormones, i.e., both the estrogens and progesterone.

stained as previously described.^{26, 65} A pretreatment endometrial biopsy, by suction curettage, was performed in the majority of patients before periods of bleeding. In our attempt to determine the effect of different doses of the hormone upon the vagina and the endometrium, biopsies were taken, in some cases as frequently as once weekly. In the routine management of a case, however, it is not essential to perform repeated biopsies, inasmuch as one can derive sufficient information, for clinical purposes, from the vaginal smears alone.



Testosterone Propionate

Dosage.—Testosterone propionate* was chosen as the most active androgen available.⁴⁸ The dosage was varied widely in the early stages of this study, in order to determine the optimal dosage required to obtain a satisfactory therapeutic effect. We had observed that menstruation can be suppressed in normal cyclical women with 500 mg. or more per month. Further experience revealed that there is a considerable variation in the response of different individuals to comparable doses of testosterone. In this series the total dosage was varied from 75 to 2,150 mg., over periods extending from one to seven months. The testosterone propionate was administered in doses of 5 to 100 mg., in sesame oil (10 to 25 mg. per c.c.), intramuscularly, 2 or 3 times weekly, in the gluteal region.

RESULTS WITH TESTOSTERONE PROPIONATE

Endometrial Studies

Preliminary premenstrual endometrial biopsies were performed in 42 cases. Of these, 4 showed hyperplasia and 4 proliferation; the remainder showed normal secretory patterns (Fig. 1).

Effect of Testosterone on the Endometrium.—As previously reported,^{21, 25, 27, 40, 63} testosterone propionate, if administered in doses of 500 mg. or more per month, may reduce the endometrium to a state of atrophy (Fig. 2) or hypoplasia. This is associated with a temporary suppression of menstruation. With smaller doses (approximately 300 to 400 mg. in one month), the corpus luteum effect on the endometrium (secretory phase) alone is suppressed with preservation of the proliferative picture, menstruation usually being delayed a few days and reduced in amount.⁶³ With still smaller doses (less than 300 mg. per month), premenstrual biopsies after testosterone propionate reveal the presence of a secretory phase, the estrogen and progesterone activity being apparently uninfluenced by the testosterone. It is noteworthy that after the discontinuation of treatment, the normal proliferative (Fig. 3) and secretory patterns (Fig. 4) of the endometrium reappear within two to three months, usually even in cases in which menstruation has been suppressed and the endometrium has been reduced to a state of advanced atrophy.

Effect of Testosterone on the Vaginal Mucous Membrane.—It has been pointed out that in large doses (500 mg. or more per month), testosterone produces striking involutional changes in the vaginal mucous membrane, coinciding with the period of induced amenorrhea.^{55, 63, 64} The smears exhibit cytologic changes indicative of varying degrees of estrogen deficiency. In some instances the involutional changes are as striking as in cases of advanced senile atrophy, the vaginal smears consisting

*For the testosterone propionate used in this investigation, we are indebted to Dr. E. Schwenk, Schering Corporation, Bloomfield, N. J. (Oreton), and to Mr. R. C. Mautner, Ciba Pharmaceutical Products, Summit, N. J. (Perandren).

after discontinuation of the treatment. At about the same time, Foss¹⁹ reported a series of 6 cases of meno- and metrometrorrhagia treated with testosterone propionate. The doses used varied from 200 to 2,200 mg. Analysis of the 6 case histories which are presented reveals that only 2 could be considered as representing satisfactory results. One patient was 45 years of age, and, after 200 mg. of testosterone, developed amenorrhea and menopausal symptoms. The other was 18 years of age and had a history of menometrorrhagia alternating with amenorrhea. On the basis of the results obtained in an additional 10 cases, the author concluded, however, that testosterone is an effective therapeutic agent in the treatment of meno- and metrorrhagia.

In the same year, Geist, Salmon and Gaines²⁵ published a series of 25 cases of menometrorrhagia (21 functional and 4 associated with small uterine myomas). The investigation included a study of the effect of testosterone propionate upon the endometrium in correlation with its clinical effects. The significance of this report is three-fold: first, the posttherapy period of observation which revealed the persistence of the therapeutic effect, in some cases for as long as five months after cessation of the treatment; second, the striking regressive changes induced in the endometrium followed by restoration to the normal pattern; and, third, the warning in regard to the induction of masculinization phenomena when large doses of testosterone are used. The dosage ranged from 300 to 1,000 mg. per month. The abnormal bleeding was controlled in all but 2 cases, during a period of observation extending up to five months. Four of the patients developed mild facial hirsuties, 3 hoarseness and one acne.

In 1938, Beclere⁶ treated 14 patients with menorrhagia (6 premenopausal, 7 associated with chronic adnexal disease, and 1 with a submucous fibroid). He was able to control the excessive bleeding in all but 2 cases (chronic adnexitis), using small doses (1 to 2 injections of 25 mg. each, per month). In 1939, the Mazers⁴⁶ obtained good results in 68 per cent of a series of 38 cases (29 metrorrhagia and 9 menorrhagia), using comparatively small doses (30 to 300 mg. per month). With this dosage no masculinization phenomena were produced.

MATERIAL

The present study was conducted on a series of 61 cases of abnormal uterine bleeding. In this series are included 25 cases which had been previously reported in 1938.

In 45 cases examination failed to reveal palpable organic disease, and the cases were accordingly classified as "functional." In 15 cases, small uterine myomas were present. These varied in size, the largest uterus approximating the size of a four months' gravid uterus. There was one case of adenomyosis of the uterus with menorrhagia. Of the 45 patients with functional bleeding, 33 were between the ages of 40 and 53 years; 11 were from 21 to 39 years of age. One patient was aged 14 years. The patient with adenomyosis was 36 years of age. Twenty-one patients had menorrhagia; 15, meno-metrorrhagia; and 9, polymenorrhea. The duration of symptoms, before the institution of treatment, varied from two months to ten years, the majority having had symptoms for more than nine months.

In the group of patients with uterine fibroids, the ages varied from 38 to 50 years. In 7, the bleeding consisted of menorrhagia; in 6, meno- and metrorrhagia; and, in 2, menorrhagia with polymenorrhea.

METHODS

Previous studies with testosterone propionate in women have demonstrated that this hormone, if given in adequate amounts, produced characteristic changes in the endometrium^{21, 25, 40, 63} (suppression of progesterone effect, inhibition of the normal proliferative picture resulting in hypoplasia or atrophy) and regressive changes (evidence of estrogen deficiency) in the vaginal smear.^{55, 63, 64} For this reason, the endometrial biopsy and the vaginal smear serve as useful objective indicators of the activity of the administered hormone and were employed in our cases in correlation with the clinical results. Smears were taken twice weekly, prepared, and



Fig. 3.—Case A. S. Endometrial biopsy (E3) taken sixteen days after the preceding one (Fig. 2), showing moderate proliferation indicative of restoration of estrogen activity.



Fig. 4.—Case A. S. Endometrial biopsy (E4), taken two weeks after E3, showing secretory pattern indicative of normal estrogen and progesterone activity. Normal menstruation began three days later.

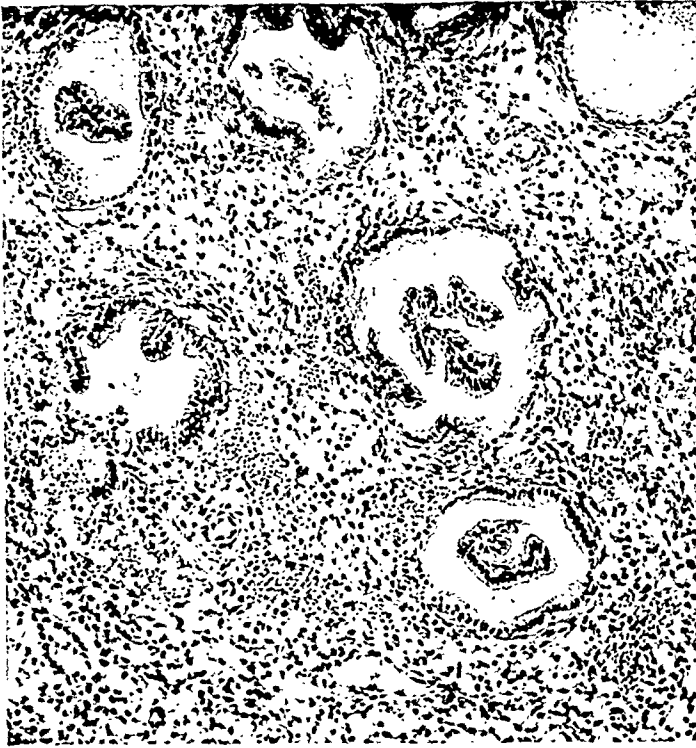


Fig. 1.—Case A. S., aged 32, gravida i, para i, had regular menstrual (28 to 30 days) cycle, menorrhagia (periods lasting nine to twelve days), fourteen months' duration. Preliminary endometrial biopsy (E1) taken two days premenstrually, showing characteristic secretory pattern. Patient was then given 650 mg. of testosterone propionate during the following thirty days.



Fig. 2.—Case A. S. Endometrial biopsy (E2) taken thirty-five days after the preliminary biopsy, i.e., five days after the expected date of onset of the next period which failed to appear. The biopsy reveals the endometrium to be in a state of marked involution.

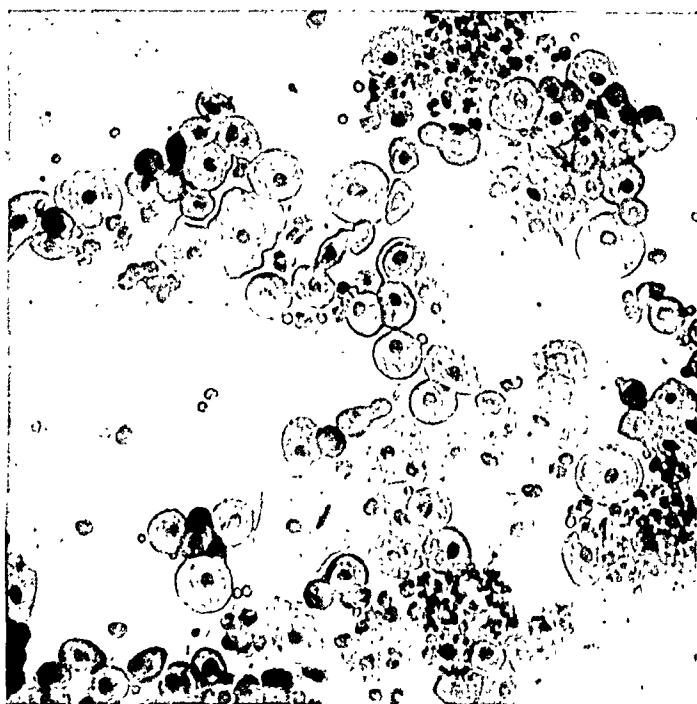


Fig. 7.—Case A. S. Vaginal smear (V3) taken ten days after V2, revealing larger epithelial cells and a decrease in leucocytes, indicating beginning estrogen activity.

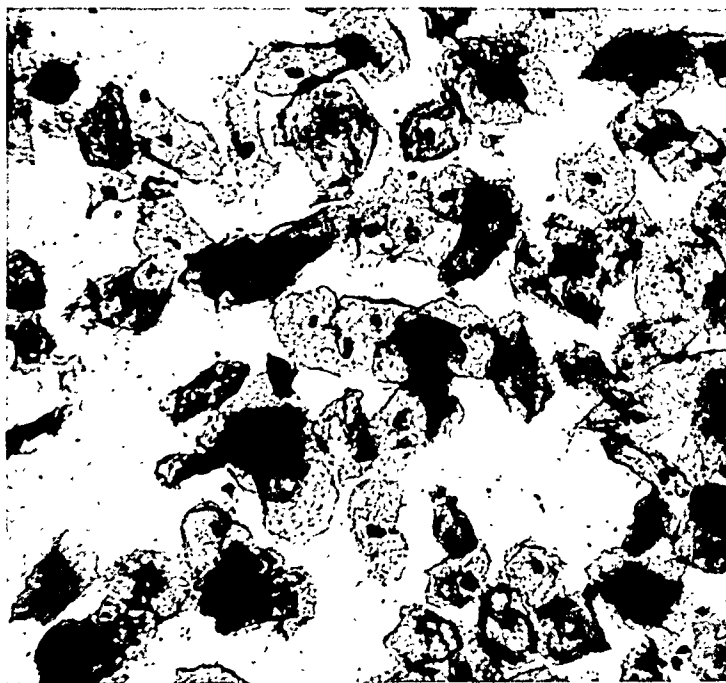


Fig. 8.—Case A. S. Vaginal smear (V4), fifteen days after V3 (which was eight days before the occurrence of menstruation). The smear shows restoration of large, squamous epithelial cells and absence of leucocytes, indicative of normal estrogen activity.

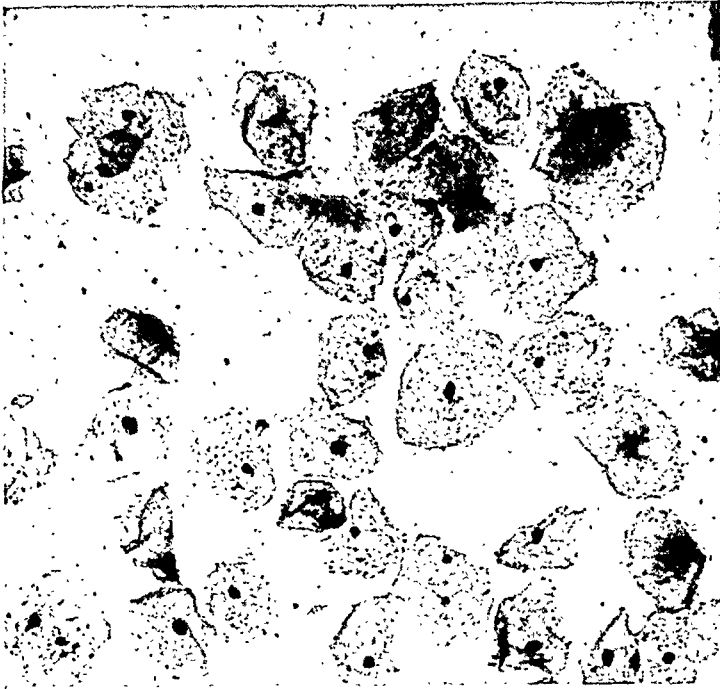


Fig. 5.—Case A. S. Normal pretreatment vaginal smear (V1), showing large, squamous epithelial cells with small, deeply-staining nuclei.

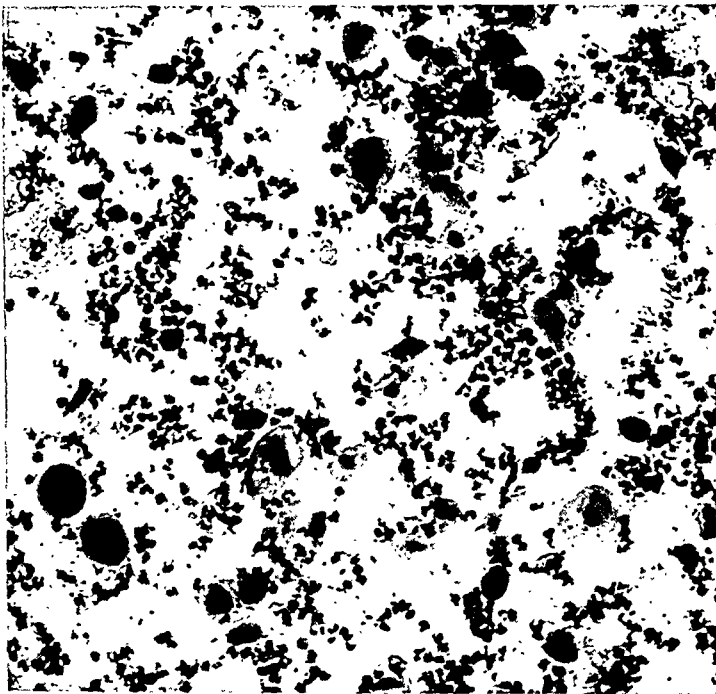


Fig. 6.—Case A. S. Vaginal smear (V2) taken at the same time as E2 (Fig. 2) during period of amenorrhea induced by testosterone propionate. The smear reveals a preponderance of small, round, and oval epithelial cells with prominent nuclei, numerous leucocytes and almost complete absence of the large squamous epithelial cells. The smear resembles the estrogen deficiency smear characteristic of senile atrophy.

RESULTS IN 15 CASES OF MENO-METRRORRHAGIA ASSOCIATED WITH FIBROIDS

Primary Results:

Temporary amenorrhea	4 cases
Normal menses	9 cases
Moderate improvement	2 cases

Late Results:

Normal menses	6 cases
Moderate improvement	2 cases
Failures	7 cases (submucous fibroids)

CLINICAL RESULTS

The results in the series of cases with uterine fibroids were not as satisfactory. The immediate results in this series were encouraging. Of 15 patients, 9 had normal, regular menses; 4, amenorrhea; 2, moderate improvement. After discontinuation of treatment, however, only 6 remained normal and regular; 2 showed approximately 50 per cent improvement; 7 had complete recurrences. Five of these patients with failures were subsequently operated upon because of the persistence of the bleeding. All were found to have submucous fibroids which probably accounted for their failure to respond to testosterone. It is worthy of note that we failed to detect in these cases any appreciable shrinkage in the size of the fibroids as a result of the treatment with testosterone.

The primary result in the case of adenomyosis of the uterus was good while the patient was receiving the testosterone. However, there was a complete recurrence of symptoms two months after the discontinuation of treatment, and hysterectomy was subsequently performed.

“ARRHENOMIMETIC” EFFECTS

Thirteen of the 61 patients in this series exhibited side-effects that are worthy of note. A number developed masculinization (arrhenomimetic) phenomena, viz., slight hirsuties of the face and extremities (5 cases), deepening of the voice (6 cases), and enlargement of the clitoris (3 cases). In 5 instances, slight acne appeared on the chest, back, and face. A few patients developed all 3 symptoms, i.e., hoarseness, hirsuties, and acne. With but one exception, *none of these complications occurred in the patients receiving less than 500 mg.* The exception was a patient who developed slight acne and hirsuties after 315 mg.

The hirsuties occurred only in brunettes, 3 of whom had had slight hirsuties before. It is interesting to note in this connection that Hamblen²⁸ has reported that brunettes excrete more androgens than blondes. The greater susceptibility of brunettes to testosterone may be related to this fact. It is worthy of note that a number of patients who received very large doses (up to 2,000 mg.) of testosterone, sufficient in many cases to suppress menstruation, did not develop any of these symptoms. The androgen effects began to regress several weeks after discontinuation of treatment, and in all but 2 cases disappeared after six months. In these two, some hoarseness and slight facial hirsuties have persisted for twelve months, but appear to be diminishing steadily up to the present writing. Both of these patients had received large doses (upwards of 1,500 mg.) of testosterone propionate.

Estrogen Deficiency Symptoms.—Several patients complained of vaginal discharge and vaginal burning during or following the testosterone administration, caused by temporary atrophic changes in the vaginal mucosa. Smears in these cases revealed morphologic changes similar to those observed in postmenopausal vaginitis. The vaginitis is probably attributable to the loss of glycogen from the vaginal mucosa.⁶⁴ These symptoms subsided rapidly after discontinuation of the testosterone propionate.

Constitutional Effects.—The majority of the patients volunteered the information that they felt more vigorous, had improved appetite and gained in weight while receiving the injections. A number of the patients, of their own volition, reported a striking increase in libido during the period of treatment.

of small, round, and oval epithelial cells with prominent nuclei ("deep cells" of Papanicolaou;⁵⁴ "atrophy cells";²⁶ "estrogen deficiency cells";* and leucocytes) (Figs. 6 and 7). In some cases the androgen effect is less marked, the smears showing only a scattering of the "atrophy cells" among the large squamous epithelial cells.

Our studies have, furthermore, revealed a fairly consistent chronologic relationship between the appearance of regressive changes in the endometrium and vaginal mucosa and the advent of the defeminization phenomena. It was noted that the latter were almost invariably preceded by the signs of morphologic regression in the vaginal mucosa and the endometrium. During the early stages of our studies, we did not fully appreciate the practical importance of this observation. Subsequently, however, it became apparent that by discontinuing the testosterone as soon as the first signs of morphologic regression made their appearance, the masculinization phenomena could be avoided. On correlating the changes in the endometrium, vaginal mucosa and vaginal smears, we found that the smears reflected the early regressive changes as consistently as the endometrial or vaginal biopsies. For this reason, we have employed the vaginal smear as an index of testosterone saturation and consider it an indispensable safeguard in regulating the dosage of testosterone in the treatment of gynecologic conditions.

RESULTS IN 45 CASES OF FUNCTIONAL BLEEDING

Primary Results:

Temporary amenorrhea	29 cases
Normal menses	15 cases
Slight improvement	1 case

Late Results (Period of Observation 6 to 38 Months):

Normal menses	26 cases
Hypomenorrhea	3 cases
Amenorrhea (menopause)	1 case
Moderate improvement	12 cases
Failures	3 cases

CLINICAL RESULTS

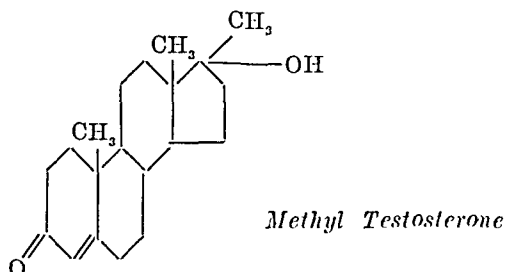
Control of excessive bleeding in the functional group occurred during, or soon after, treatment, in all but one case. Good primary results occurred, therefore, in 97.7 per cent of the cases. In many instances, improvement became apparent after one month; in others, only after two or three months of treatment. In 29 cases, a temporary amenorrhea of one and one-half to four months was first established, followed by normal menses. In 26 cases a normal menstrual cycle was established and persisted during the entire period of observation which, in several cases, extended up to thirty-six months. In 5 of this group, moderate menorrhagia returned several months after the discontinuation of the treatment. These patients were controlled with supplementary courses of testosterone for one or two months, the monthly dosage varying from 100 to 200 mg. In 3 cases, there was complete recurrence of the menorrhagia after intervals of six, eighteen, and twenty months' duration, respectively. One woman, 50 years of age, developed amenorrhea and menopausal symptoms. Three others, also in the fifth decade of life, showed alternating periods of hypomenorrhea and amenorrhea. In 12, the bleeding, though not restored to normal, was considerably diminished in amount and duration. Thus, after a follow-up extending up to thirty-six months, satisfactory results persisted in 66.6 per cent of the cases and moderate improvement in 26.6 per cent. The remaining 6.8 per cent of the cases were considered therapeutic failures.

*We have suggested calling these cells "atrophy" or "estrogen deficiency" cells, since their presence in the smear is the result of some degree of atrophy of the vaginal mucous membrane and is indicative of a state of estrogen deficiency.

RECENT ADVANCES IN ANDROGEN THERAPY

Although the clinical results obtained with testosterone propionate in the treatment of functional bleeding have been satisfactory, the treatment has two objectionable features. These are: (1) the necessity for repeated injections, and (2) the risk of inducing arrhenomimetic phenomena.

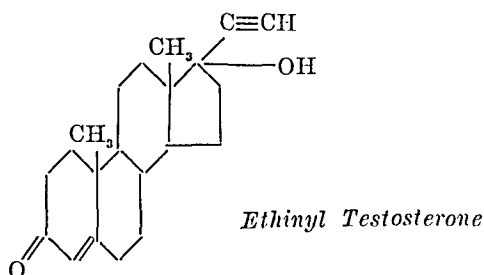
Oral Administration of Androgens.—In an attempt to overcome the first of these, we have resorted to two other methods of administering androgens, i.e., by the oral route and by implantation of pellets of the hormone. Testosterone and testosterone propionate are absorbed in such small amounts from the intestinal tract that enormous doses would have to be administered in order to be effective. The expense to the patient would be so great as to make it impractical.



Methyl testosterone,^{20, 58} however, is absorbed much more readily from the intestinal tract. In a study of the biologic properties of this compound, we have found that when administered enterally its effects are very similar to those produced by testosterone propionate given parenterally.³⁵ Its androgenic potency in women (when given by mouth) appears to be approximately one-third that of testosterone propionate administered intramuscularly. Although our clinical studies with this compound have not been extensive enough to warrant final conclusions, we have sufficient data to lead us to believe that this compound should prove valuable as a therapeutic androgen.

Buccal Absorption of Testosterone in Propylene Glycol Solution.—Recently we have found that testosterone in solution in propylene glycol is absorbed from the sublingual space. Preliminary studies indicate that this may prove to be a simple and economical method of androgen administration.

Implantation of Androgen Pellets.—With the objective in view of eliminating frequent injections, we implanted 22 patients with pellets of testosterone and testosterone propionate.³⁶ The results of this study are being reported in detail elsewhere. Although some very interesting information was obtained concerning the rate of absorption of the hormone and its effect upon the surrounding tissues, the implantation of testosterone appears to be of little, if any, practical value as a therapeutic procedure in gynecology.



VALUE OF METHYL TESTOSTERONE

In an attempt to find a therapeutic agent that would possess the therapeutic effectiveness of testosterone propionate without its arrhenomimetic properties, we have used a number of androgens of low androgenic potency, viz., androstenedione,

Effect of Testosterone Propionate on Associated Dysmenorrhea, Premenstrual Tension and Mastalgia.—A number of patients who had dysmenorrhea, premenstrual tension, and premenstrual mastalgia, associated with menorrhagia, reported either considerable improvement or complete relief.

MANAGEMENT OF A CASE OF MENO- AND METRORRHAGIA WITH TESTOSTERONE PROPIONATE

During the experimental stage of our investigation, the dosage of testosterone propionate was varied widely in order to reveal the range of its biologic and therapeutic effects. Accordingly, we have been able to study the clinical, as well as the morphologic, results of doses varying from 45 to 1,000 mg. per month. It soon became apparent that in order to attain a therapeutic effect, it was not necessary to resort to the high doses. Whereas, in the cases in which marked inhibition of the endometrium and temporary suppression of menstruation were induced, good results were achieved, it is significant that comparably good results were obtained in other patients with doses insufficient to suppress menstruation or to produce morphologic evidence of estrogen deficiency in the endometrium and vaginal mucosa. There is undoubtedly a considerable variation in the responsiveness of different individuals to similar amounts of testosterone propionate. This is probably due to variation in the androgen requirements of different individuals.

Until we are able to determine, quantitatively, the androgen needs of the patient, and, in the absence of methods of estimating, individual susceptibility, we deem it advisable to adhere to certain more or less arbitrary limitations of dosage. Each patient must, furthermore, be considered in the light of an individual experiment. It may be necessary to increase or decrease the amount administered, depending upon the response of the patient. Endometrial biopsies and vaginal smears (both of which are office procedures) are of considerable aid in the regulation of the dosage.

Severe Meno- and Metrorrhagia.—For patients with marked bleeding, we suggest 300 mg. per month as the optimal dose, given in single intramuscular injections of 25 mg., 3 times weekly. Vaginal smears should be taken twice weekly and, at the first sign of regressive changes, therapy should be discontinued. If there is no, or only slight, symptomatic improvement during the next menstrual period, a similar course of testosterone should be repeated the following month. If the first menstrual period is moderately improved, 150 mg. in divided doses may be given the following month. If the bleeding is reduced to approximately normal after the first course, a second course should be given the following month, reducing the monthly dose to 100 mg.

Moderate Meno- and Metrorrhagia.—For patients with moderate degrees of menorrhagia or menometrorrhagia, 150 to 200 mg., in divided doses, for the first month, is usually adequate. It is advisable to supplement the first month's treatment with a second course the following month, using approximately half of the first monthly dose.

Patients that have shown a tendency to recurrence after an interval of normal menses for several months have been satisfactorily controlled with small doses, e.g., 10 mg., twice or three times weekly, or 25 mg. once weekly, given for four to six weeks.

If menstruation is suppressed or delayed, the further management of the case is determined by the endometrial biopsy and vaginal smear findings. If the endometrial biopsy reveals absence of secretory phase of regression of the proliferative phenomena and/or the vaginal smear shows estrogen deficiency changes, no more testosterone should be given. If at any time during the course of treatment facial hirsuties or coarsening of the voice should occur, therapy should be discontinued. Should acne occur, it need not be considered a serious deterrent to further therapy, since it subsides rapidly after stopping the testosterone. We have found it helpful to use an ointment containing estrogens, locally, in these cases (360 R.U. of estradiol per gram of lanolin base). The vaginitis that may occasionally occur can be readily controlled with vaginal estrogen suppositories (2,500 R.U. of estradiol [progynon DH] per suppository) used nightly for several nights.

In any event, it appears from these studies that menorrhagia and metrorrhagia, associated with submucous fibroids, are not satisfactorily controlled by testosterone, whereas, in the presence of small or intramural fibroids, the results are likely to be as satisfactory as in the purely functional group.

Undesirable Effects.—Under this caption are included masculinization (arrhenomimetic) phenomena and the estrogen deficiency symptoms which result from large doses of testosterone. As has been pointed out above, this syndrome, viz., the amenorrhea, hirsuties, hoarseness, and enlargement of the clitoris, is induced when doses of 500 mg. or more per month are administered. The therapeutic dose is considerably smaller and, with the exception of an occasional susceptible case, produces none of these complications. It is, furthermore, possible to avoid these phenomena, even in the susceptible cases, by paying close attention to the cytologic changes in the vaginal smear. At the first sign of androgen effect, the testosterone should be discontinued. If this safeguard is employed, the valuable therapeutic properties of testosterone can be utilized without fear of inducing any of the undesirable arrhenomimetic phenomena.

Relationship to Fertility.—The question may be raised whether testosterone may interfere with fertility. It is logical to assume that when sufficient testosterone propionate is given to abolish the progesterone effect in the endometrium and to suppress menstruation, ovulation has probably been inhibited. Furthermore, histologic studies²⁴ of the ovaries of women, with normal ovulatory cycles, who had been injected with large doses of testosterone propionate, indicated that maturation of the follicle and ovulation are inhibited. It is worthy of note that excretion of pregnanediol was suppressed during the current cycle in these cases.³⁴ The regular reappearance of the secretory phase in subsequent cycles indicates, in the light of our present knowledge, the resumption of the normal gonadotropic activity by the pituitary and restoration of normal follicle growth and ovulation with its attendant hormone production. In one case, following the administration of large doses of testosterone propionate (sufficient to suppress menstruation and induce characteristic regressive vaginal smear changes), conception took place during the period of amenorrhea and within two weeks after the return of the smear to its normal (follicular) status. This patient was delivered of a normal child nine months later and, during the succeeding twenty-four months, has had normal regular cycles. There have been 2 other normal pregnancies in this series. Mazer and Mazer⁴⁶ reported 4 pregnancies following testosterone therapy. Of these, one patient had an induced abortion, and 3 were delivered of normal infants.

Modus Operandi of Testosterone Propionate.—The hormonal mechanisms involved in normal, as well as in abnormal, uterine bleeding are still but incompletely understood. Any discussion, therefore, of the modus operandi of a therapeutic agent that is presumed to control abnormal uterine bleeding must be regarded as highly speculative. However, a few facts are known and, on the basis of these and our knowledge of the biologic effects of testosterone in women, we are prompted to formulate a theory concerning the mechanism of the testosterone action.

androstenediol and ethinyl testosterone. The first two proved disappointing; the last seemed to possess therapeutic potentialities. This compound (ethinyl testosterone; pregneninolone; Δ^4 pregnenin-20-on-3-ol-17; anhydro-hydroxy-progesterone), which was synthesized by Inhoffen, Longemann and Serini³² and is structurally very closely related to testosterone and progesterone, has been shown to possess the following biologic properties: (a) a progesterone-like action (progestomimetic) in immature rabbits (being active when administered orally);^{33, 59} (b) an estrogen-like action (estromimetic) on the uterus and vagina of adult and immature rats;^{17, 66} and (c) an androgen-like action (andromimetic) in capons and rats.^{13, 17, 66}

In human beings, this compound has been shown to produce a progestational effect on the estrogen-primed endometrium;^{10, 67} to be very weakly estromimetic and to exhibit no arrhenomimetic properties.⁶⁸ There have been but few reports of the clinical use of this compound. Zondek and Rozin^{74, 75} have reported induction of uterine bleeding with pregneninolone; Hamblen²⁹ has investigated its value in the treatment of functional uterine bleeding with equivocal results. We have used this compound for a period of eighteen months in both functional meno- and metrorrhagia²² and dysmenorrhea.^{35, 69} Although the dysmenorrhea was relieved in a number of patients, pregneninolone appeared to have no significant effect on the abnormal bleeding.

DISCUSSION

A number of questions arise with regard to the use of testosterone in the treatment of abnormal bleeding, questions relating to (a) its efficacy as a therapeutic agent; (b) the undesirable effects that may result from its use; (c) the modus operandi; and, as a corollary to the last, (d) the theoretical implications as to the role played by androgens in the causation of normal and abnormal uterine bleeding.

Therapeutic Efficacy.—It is apparent from the results reported here that very satisfactory results can be obtained with testosterone propionate in the treatment of some types of functional uterine bleeding. The persistence, furthermore, in the majority of the cases, of a normal menstrual cycle for many months after discontinuation of the treatment, prompts us to recommend testosterone propionate as a very effective and satisfactory therapeutic agent in the treatment of functional uterine bleeding.

In contrast to the high percentage of good results obtained in the functional group, comparatively poor results were noted in the patients in whom bleeding was associated with fibroids. The initial results in the group with fibroids were quite good. However, after the discontinuation of testosterone, menstruation remained normal in only 6 of the 15 patients. In 6 patients, the abnormal bleeding recurred completely. Four of these were subsequently operated upon and found to have submucous fibroids.

Are we to attribute the failure in these cases to the presence of the submucous fibroids? It is, of course, unsatisfactory to draw conclusions from so small a number of cases, but, based on the results of this series, the conclusion seems warranted that when abnormal uterine bleeding is associated with submucous myomas, testosterone is not likely to have more than a temporary effect.

As regards the patients with small fibroids in whom abnormal bleeding was completely controlled, it is an open question whether the excessive bleeding was attributable to the small fibroids or to the same etiologic factors which cause excessive bleeding in the functional group.